Publication Series
INTERDISCIPLINARY PLATFORM ON BENEFIT ASSESSMENT

Volume 17
September 2023

Impact of EU HTA on the AMNOG procedure

Springer Medizin

PUBLICATION SERIES INTERDISCIPLINARY PLATFORM ON BENEFIT ASSESSMENT

VOLUME 1
Four years of AMNOG – Discourse and impulses

VOLUME 2
Clinical studies – Which endpoints count?

VOLUME 3
Adaptive Pathways – Opportunities and risks

VOLUME 4
AMNOG 2.0 – Information problems

VOLUME 5
Evidence gaps – What does registry data offer?

VOLUME 6
Physician information via software – Ways and goals

VOLUME 7
Physician information via software – Orientation or control?

VOLUME 8
European Benefit Assessment – Opportunities and risks

VOLUME 9
Contextual evidence – Strategies for targeted therapy

VOLUME 10
What are the (additional) benefits of registry data?

VOLUME 11
European HTA Procedure – Advances and pitfalls

VOLUME 12
Digital health data: Benefits, costs, governance

VOLUME 13
Patients and medical societies: Additional expertise for AMNOG

VOLUME 14
Guidelines – their role in AMNOG and medical care

VOLUME 15
Further development of the AMNOG with a sense of proportion and evidence

VOLUME 16
AMNOG: Financial stabilisation – new treatment paradigms

VOLUME 17
Impact of EU HTA on the AMNOG procedure

ALL VOLUMES AVAILABLE ONLINE AT:
HTTPS://WWW.AERZTEZEITUNG.DE/KOOPERATIONEN/PLATTFORM-ZUR-NUTZENBEWERTUNG

Volume 17
September 2023

Contents

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

European benefit assessment: AMNOG must once again prove to be a learning system

Professor Jörg Ruof

Dear readers

This is the third time that the Platform for Benefit Assessment deals with the topic of EU HTA. In publication 8 of March 2019, the opportunities and risks of a European benefit assessment were weighed up, and in publication 11 of September 2020, progress and pitfalls were analysed. In January 2022, the corresponding EU HTA regulation finally entered into force. Accordingly, we are taking a new perspective in the current publication. It is based on the question of what effects or repercussions the European HTA assessment that shall be implemented step by step, has on the German AMNOG procedure.

The format of the platform meeting was adapted. After a set of three presentations each, the speakers were asked questions prepared by Frank-Ulrich Fricke and Christian Dierks, respectively. Only then did the general plenary discussion take place, which was summarised by Florian Staeck. The first set of three presentations presented an overview of the perspective of the „Heads of HTA Agencies" (Marcus Guardian), the G-BA (Antje Behring), and the regulatory authorities (Bettina Ziegele).

The second set of presentations focused on the methodological aspects with contributions from IQWiG (Stephan Lange), professional societies (Bernhard Wörmann) and the industry (Sandro Gsteiger). The external view from an Italian-American perspective by Luca Pani and Heiner Bucher with a methodological case analysis on avapritinib complements the thematic blocks.

It becomes apparent that the national HTA processes across the various EU member states are extremely heterogeneous. Methodological bases, implementation and capacities for early consultations, timelines and process elements of the national HTA processes and ultimately the duration until the availability of innovative medicines for affected patients differ considerably between the member states. As a large and economically leading EU Member State, Germany has a dual role: i) to contribute to the shaping and implementation of the EU HTA regulation and ii) to swiftly implement the European requirements in the national processes.

- IQWIG and the G-BA are very actively involved at the European level through their participation in the coordination group in the context of methods development and in the Joint Scientific Consultation.
- Conversely, with regard to the implementation of the EU requirements in the national AMNOG system, the following initially applies – as formulated by the Federal Government in response to the minor interpellation from the CDU/CSU parliamentary group in May 2023: „The national AMNOG process of benefit assessment according to § 35a SGB V and subsequent negotiation of the reimbursement amount according to § 130b SGB V has proven its worth and should be retained as far as possible with the aim of continuing to ensure rapid access for patients to new pharmaceuticals." (https://dserver.bundestag.de/btd/ 20/ 069/2006930.pdf)

The rapid access of patients to new pharmaceuticals, which is exemplary throughout Europe, is to be welcomed in any case. On the other hand, in terms of agility, it is desirable that essential additions are made to the AMNOG procedure in the course of the procedure, e.g. regarding the scope and structure of the dossiers or the prospective harmonisation of methodologically controversial points, e.g. with regard to elements of the PICO scheme.

The role of EU HTA is outlined in the EU HTA regulation as follows: „HTA CAN [author's emphasis] contribute to the promotion of innovations that deliver the best possible outcomes for patients and society at large, and provides the means to ensure the correct application and use of health technologies." (https://eur-lex.europa.eu/ legal-content/EN/TXT/PDF/?uri=CELEX:32021R2282)

It remains to be seen to what extent this „CAN" requirement will become reality. A promotion of innovation, an approximation to this vision of HTA and ultimately also a strengthening of Europe in global competition will only be possible if the AMNOG once again proves itself to be a learning system and takes on a pioneering role in Europe. Ultimately, the goal is that – over time – the underlying processes, methods, and values (i.e. a uniform definition of a relevant added benefit) will be harmonised in Europe beyond the individual requirements of the law.

Enjoy reading the exciting articles of this publication.

Contact:
joerg.ruof@r-connect.org

Quo vadis, HTA? Major discussion points with the speakers

Professor Frank-Ulrich Fricke | Faculty of Business Administration TH Nürnberg Georg Simon Ohm, Member of the Arbitration Board according to § 130b SGB V

The Regulation 2021/2282 of the European Parliament and the Council dated 15 December 2021, was the starting point for the preparations for a joint clinical evaluation of health technologies in Europe. According to the regulation, the objectives of the joint clinical evaluation are to improve clinical decision-making, pool the expertise and resources of national HTA authorities and bodies, ensure health protection for patients and users as well as a smooth functioning of the internal market with regard to health technologies, avoid duplication of work among health technology developers and evaluation institutions, promote innovation, and ultimately provide faster access to innovative health technologies for all people in the European Union.

Joint Clinical Assessment (JCA) is the scientific analysis of improvements in new health technologies compared to comparator therapies, which may be different among the member states in terms of clinical/patient outcomes. Thus, the uncertainty as a consequence of the underlying evidence, and consequently the quality of the evidence, should be taken into account.

The methods and processes for conducting the joint clinical evaluation are currently being developed and will be further developed in the coming years. The evaluation will start in 2025 for the following three years with new health technologies from oncology and/or advanced therapy medicinal products (ATMPs) under Regulation 1394/2007 of the European Parliament and of the Council. Orphan drugs will then follow from 2028, and as of 2030, all pharmaceuticals in the European Union's centralised marketing authorisation will be subject to joint clinical evaluation.

Professor Frank-Ulrich Fricke *is Professor of Health Economics at the Nuremberg University of Applied Sciences Georg Simon Ohm and an impartial member of the Arbitration Board according to § 130b SGB V. After studying business administration and receiving a doctorate in economics, he worked in the pharmaceutical industry and in consulting for several years. Major topics in consulting were questions of market access of diagnostic and therapeutic innovations, health economic evaluations and questions of benefit assessment and reimbursement pricing as well as health policy and health system development. Professor Fricke is a member of various national and international professional societies.*

Against this background and in light of the three presentations by Marcus Guardian (Status of the EU HTA – on the path to harmonisation?), Antje Behring (EU HTA – What will change from a national perspective?) and Bettina Ziegele (Early Regulatory Advice & Collaboration with EU HTA), the following three sets of questions were discussed during the panel discussion:

Implementation

- *What is the current state of the development?*
- *What difficulties have emerged in the process?*
- *Will all relevant information for conducting the assessment be available at the start of the first assessments in 2025?*
- *Is the development process fast enough?*
- *Will the European assessment rules have to be included in the national rules or can they be included at all?*
- *What experience from the EMA's joint approval procedures can be integrated into this development process?*
- *How should we deal with the uncertainty about the usability of the results of the joint European evaluation in national procedures?*

Methodological requirements

- *When can methodological guidelines or guidance for the conduct of the joint clinical evaluation be expected?*
- *How will the needs of the evaluation institutions of the member states be taken into account in the joint evaluation?*
- *What will be the results of the „scoping", i.e. the determination of the evaluation questions (PICO, Population, Intervention, Comparison, Outcome)?*
- What will the collaboration with the EMA look like?

Objectives and target horizon

- *When can full harmonisation be expected in Europe?*
- *How long do we have to expect additional efforts for the European procedure in addition to the national procedures?*
- *What is the timing of the European and national procedures?*
- *Will the national procedures be able to incorporate the results of the European procedures?*

Status of the EU HTA – on the path to harmonisation?

Marcus C. Guardian | EUnetHTA21 Chief Operations Manager, Heads of HTA Agencies Group (HAG), General Manager, International Horizon Scanning Initiative (IHSI), General Manager

The European regulation on Health Technology Assessment (HTA) came into force at the beginning of 2022. After a preparatory phase, newly approved oncology or ATMP products (Advanced Therapy Medicinal Products) will be subject to a Joint Clinical Assessment at European level from 2025. From 2028, the spectrum will be expanded to include all orphan drugs and from 2030, all pharmaceuticals will be included. The final appraisal remains the responsibility of the EU member states. Whether the EU HTA regulation will ultimately lead to a harmonisation of the different national assessments remains to be seen. Based on experience with the introduction of the central European authorisation EMA, convergence of the HTA procedures based on the EU HTA regulation can certainly be assumed; what is more questionable is the duration of this process and how many and which intermediate steps required on this path.

Introduction of the EU HTA Regulation

The European Regulation 2012/2282 of the European Parliament and of the European Council of 15 December 2021 on Health Technology Assessment (HTA) came into force on 11 January 2022. It provides for a three-year preparatory phase, so that the envisaged common European HTA procedure will be applied for the first time as of 12 January 2025.[1]

This was preceded by many years of intensified cooperation between HTA organisations across Europe within the framework of several Joint Actions funded by the European Commission (JA1, JA2, JA3). An overview of this history of the European Network for Health Technology Assessment (EUnetHTA) was presented at the Interdisciplinary Platform on Benefit Assessment in spring 2020 and published.[2]

Regulation 2012/2282 comprises an extensive (58 paragraph) introductory part and the actual legislative text. The latter describes the details of the European HTA assessment in 36 articles or 5 chapters, respectively:

i) General Provisions
ii) Joint Work on Health Technology Assessment at Union Level
iii) General Rules for Joint Clinical Assessments
iv) Support Framework
v) Final Provisions. The explanations on the Joint Clinical Assessment (JCA, Articles 7-15 of the Regulation) and Joint Scientific Consultations (JSCs, Articles 16-21 of the Regulation) play a significant role.

Accordingly, from 2025, centrally newly authorised pharmaceuticals in the field of oncology or ATMP products (Advanced Therapy Medicinal Products) will be subject to a Joint Clinical Assessment. From 2028, the spectrum will be expanded to include all orphan drugs and from 2030, all pharmaceuticals will be included. Also included in the re-

gulation are class IIb or III medical devices as well as class D in vitro diagnostics. In an obvious parallel to the authorisation procedure of the European Medicines Agency (EMA), the scientific review of the dossier submitted by the manufacturer is carried out by an assessor and a co-assessor from the EU member states. The JSCs, on the other hand, are carried out by the HTA Coordination Group itself – in each case in cooperation with the EMA.

According to the EU HTA regulation, there is a differentiation of the responsibilities of the EU HTA assessment versus the national appraisals in the member states (see figure 1). In terms of content, various aspects are considered: within the framework of the EU assessment, the clinical domains are assessed, while national appraisals focus on the non-clinical domains. According to the regulation, a double presentation of identical clinical data both within the framework of the EU assessment and in the national procedures in the member states shall be excluded; however, there is the option at national level to include additional clinical data in the appraisal, e.g. for another comparative therapy or data from national healthcare registers that have not yet been presented at EU level.

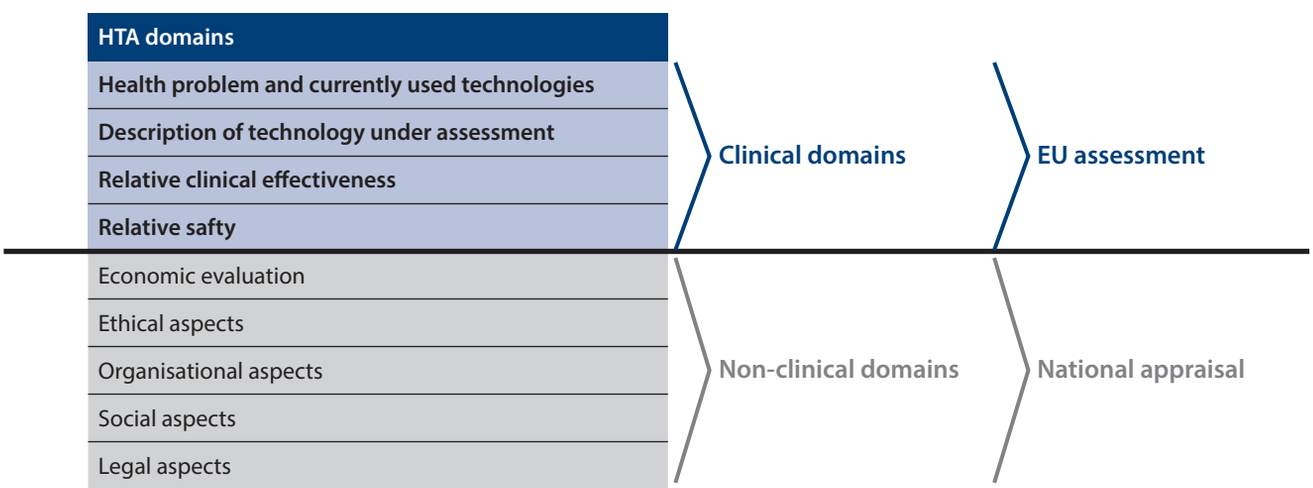
Marcus C. Guardian *pursued a career in network development, strategic leadership and policy management after studying international law at TU Dresden and business administration at Qingdao University and diplomatic studies at Leicester University. In 2016, he took over as COO (Chief Operating Officer) for the operations of the third EUnetHTA Joint Action 3. Since 2021, he has led the successor organisation EUnetHTA 21. In parallel, he launched the International Horizon Scanning Initiative (IHSI) and took over the leadership of the Heads of HTA Agencies Group*

Stepwise introduction of EU HTA regulation

Figure 2 provides an overview of the different phases of the introduction of EU HTA regulation. The main activities of the preparatory phase include the establishment of the HTA Coordination Group (HTACG) with the four subgroups: i) methodological and procedural guidance; ii) joint clinical assessment; iii) joint scientific consultations; iv) identification of emerging health technologies.

At the beginning of April 2023, the updated Rolling Implementation Plan of the European Commission was published.[3] This presentation shows that the HTACG has been active since June 2022 and that these four subgroups first met in April 2023. At its November 2022 meeting, the HTACG elected Dr Roisin Adams of the National Centre for Pharmacoeconomics in Ireland as its Chair. One important activity of the HTACG remains the production of guidance documents on the process and methodology of EU HTA assessments. Until September 2023, the HTACG will be supported by the EUnetHTA21 consortium, which has already developed and published a large number of corresponding documents. EUnetHTA 21 is working on behalf of the European Commission, which will then make the corresponding deliverables available to the HTACG. An overview of the status of the development of the guidance documents by EUnetHTA21 can be found on their website (see figure 3).[4]

Focus of the EU assessment compared to the national appraisals in the member states



Source: Marcus Guardian

Figure 1: Clinical domains are assessed in the EU assessment. In contrast, appraisals in EU member states focus on non-clinical issues.

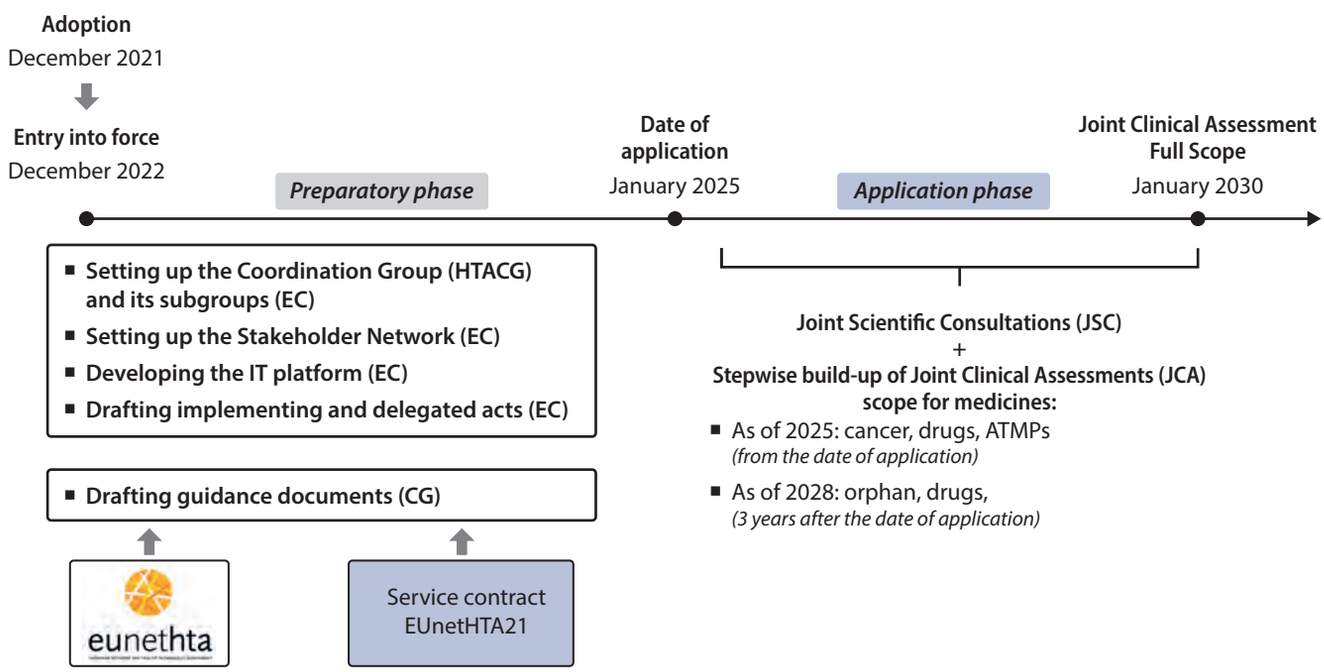
Further activities in the preparatory phase include creation of a stakeholder network. The corresponding call for proposals was published by the European Commission in December. The deadline for applications was February 2023; the final selection of participants in the stakeholder network has not yet been published.

The development of an IT platform is anchored in Article 30 of the EU HTA Regulation and represents another focus of the European Commission in the preparatory phase. Finally, the preparation of Implementing and Delegated Acts is planned until 2025. These laws include, in particular, detailed explanations and regulations on JSCs and JCAs for both pharmaceuticals and medical devices, as well as regulations on dealing with conflicts of interest and on data protection and confidentiality, especially when exchanging information with the EMA (see figure 3).

The timeline to fulfil all the required activities by 2025 is very tight. Currently, half of the preparatory phase has already passed. A survey conducted by the European Access Academy shows that there are still considerable limitations both in terms of the readiness of the individual EU Member States and capacity bottlenecks on the part of the EU level.[5]

From 2025, the EU HTA regulation will be applied in practice. Initially, the assessment will be carried out for oncology products and ATMPS, but in 2028 orphan drugs will also be subject to an EU HTA assessment. From 2030, the full assessment scope is envisaged, i.e. all newly approved pharmaceuticals will then be subject to EU HTA assessment.

Timeline for the introduction of the EU HTA Regulation



Source: Marcus Guardian

Figure 2: The introduction of EU HTA regulation will take place in several steps. Only from January 2030 will all newly authorised pharmaceuticals then be subject to the regulatory regime of the EU HTA assessment.

European Health Technology Assessment on the way to harmonisation?

With the introduction of the EU HTA regulation, structures and processes will first be established at the European level that will gradually enable a central assessment of new medicines. Figure 4 presents the interaction of these European HTA structures.

The HTACG will play a significant role in future. It will be responsible for the future EU HTA assessments. The secretariat at the Commission will only have a coordinating function. The work of the HTACG will be supported by the cooperation at regional level, e.g. in the Nordic countries or in Benelux. Furthermore, a Heads of Agency Group (HAG) of the various HTA bodies of the member countries has been formed – analogous to the approval – which is responsible for the implementation of the regulation.

The cooperation of the HTA bodies of the individual Member States will be essential for a successful introduction of the regulation. On the one hand, they are required to actively participate in the assessments as assessors and co-assessors; on the other hand, they are responsible to use the EU HTA Assessment Report against the back-

Overview of Implementing Acts of the EU HTA Regulation

Subject matter	Legal basis
JCA medicinal products (detailed procedural rules, format and templates, stakeholder involvement, selection and consultation of experts, EMA cooperation)	Articles 15(1)(a), 15(1)(c), 25(1)(b) and 26(1) HTAR
Conflict of interest assessment and management	Article 25(1)(a) HTAR
JSC medicinal products (submission of requests from HTDs, stakeholder involvement, selection and consultation of experts, EMA cooperation)	Articles 20(1)(a), 20(1)(b) 20(1)(c) HTAR
JCA medicinal devices (detailed procedural rules, format and templates, stakeholder involvement, selection and consultation of experts, cooperation NB & expert panels)	Articles 15(1)(b), 15(1)(c), 25(1)(b) and 26(1) HTAR
JSC medical devices (submission of requests from HTDs, stakeholder involvement, selection and consultation of experts, cooperation expert panels)	Articles 20(1)(a), 20(1)(b) and 20(1)(d) HTAR
General **confidentiality arrangements** for the exchange of information with EMA (related to JCAs, JSCs, horizon scanning etc.)	Articles 15(1)(a), 15(1)(b), 20(1)(c) and 20(1)(d) HTAR

Source: Marcus Guardian

Figure 3: The draft of the Implementing and Delegated Acts is scheduled by 2025. These will primarily concern explanations on JSCs and JCAs as well as regulations on dealing with conflicts of interest and confidentiality.

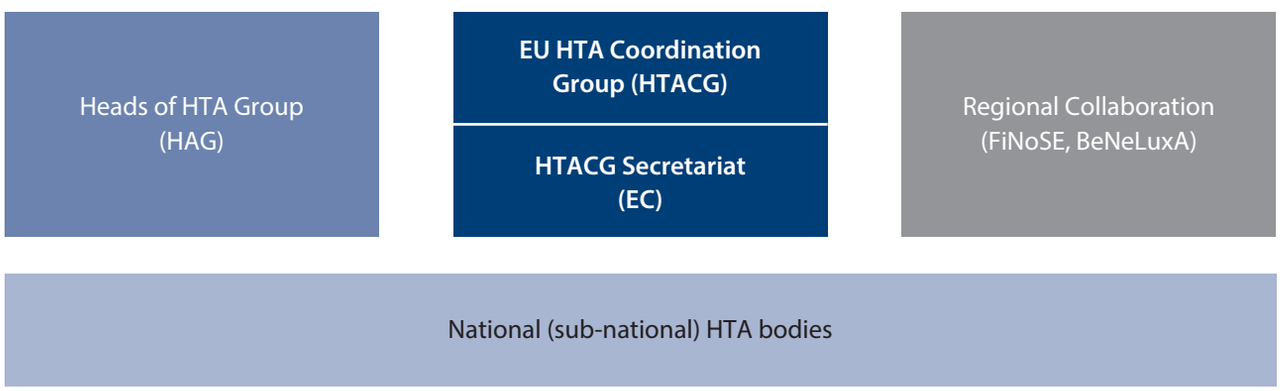
ground of the national specifics and – if necessary – complement it accordingly.

It remains to be seen whether the EU HTA regulation will ultimately lead to a harmonisation of the different HTA assessments of the EU member states. The experience with the introduction of the central European authorisation EMA seems to be interesting. Wiebke Löbker and Karl Broich report how the assessment processes and standards of clinical evidence within the framework of the risk-benefit assessment of pharmaceuticals in Europe have been harmonised to a large extent over many intermediate steps.[6] In this sense, a convergence of the HTA procedures on the basis of the EU HTA regulation can certainly be assumed in the long term. However, it is questionable what time this process will take and how many and which intermediate steps are needed for this process.

Disclaimer

The views expressed in this article are those of the author and do not reflect the views of the Dutch National Institute of Health (ZIN), the EUnetHTA21 consortium, the Heads of Agency Group or the European Medicines Agency (EMA) or its committees or working groups.

European HTA structures



Source: Marcus Guardian

Figure 4: The HTA Coordination Group (HTACG) with its four subgroups plays a central role in the interaction of the European HTA structures.

References

[1] https://go.sn.pub/bdMgas

[2] Guardian M. Benefit Assessment and Early Advice of EUnetHTA. Publication series Interdisciplinary Platform on Benefit Assessment Volume 11; September 2020. European HTA process. Progress and pitfalls. p. 24-31.

[3] https://go.sn.pub/Mnkpzs

[4] https://go.sn.pub/rRk2L7

[5] EAA Convention Proceedings. Volume 3, April 2023. Midterm & Status of the Preparation Phase of the EU HTA Regulation. www.euaac.org.

[6] Löbker W, Broich K. Harmonised HTA assessment: Experiences on the way to centralised approval Publication series Interdisciplinary Platform on Benefit Assessment Volume 8; March 2019 p. 52-61.

What impact will EU HTA have on the AMNOG process?

Dr Antje Behring | Head of the Medicines Division at the Federal Joint Committee (G-BA)

The HTA regulation that came into force in 2022 established the legal basis for the previously voluntary European HTA collaboration. Consequently, procedural adjustments will be required in the AMNOG process and will influence the deliberations of the G-BA. Despite the remaining uncertainties regarding the implementation of HTA regulation, an EU benefit assessment offers added value for the whole of Europe: the evidence preparation for the different questions of the member states is available to all stakeholders. Through this transparent and inclusive process, subsequent assessments can be better understood by the different health systems.

Introduction

The introduction of a European HTA system was one of the central goals of European health policy until the outbreak of the corona pandemic. In the aftermath of the pandemic, many health systems are more than ever under hardly manageable cost pressures and the impression that some decisions should have been taken differently based on superior data. Although HTA can in principle support benefit-cost trade-offs by providing evidence – as long as evidence is available – the capacities available at European and national level are scarcer than ever.

In the transitional project EUnetHTA21 discussions are currently taking place about the future EU HTA process as to how this could possibly proceed under EU HTA regulation. These discussions serve to identify challenges for the subsequent joint clinical evaluations and scientific consultations of medicinal products or medical devices at an early stage and propose suitable solutions. The participating HTA agencies in EUnetHTA21 are working with a common concrete objective for the first time based on a common legal foundation: the EU HTA Regulation.

The implementation of this regulation requires adaptations in all member states: on the one hand, recognised HTA systems have to adapt and, on the other hand, other member states that did not perform HTA so far have to establish a system for the use of HTA reports. The mutual exchange for a common understanding of HTA, regulation, design of procedural rules and sometimes just understanding of terminology was and is of enormous importance for the preparation of the regulation.

Differences in reimbursement systems across Europe

National assessments that precede reimbursement decisions are not easily comparable. Looking at the evaluation of medicines, most member states use health economic mo-

delling using cost-effectiveness analyses. Only about one third, including Germany, limit themselves to pure relative clinical effectiveness analysis. In a very small area, a full HTA assessment is performed, i.e. including clinical effectiveness, economic analyses, but also incorporating legal, ethical, and social aspects.[1]

However, Germany is the only country in which the market launch of a pharmaceutical is not tied to previous evaluations and negotiations; instead, the pharmaceutical can be prescribed and reimbursed directly at the expense of the health insurance fund once it has been listed in a pharmaceutical directory. Unlike in Germany, in other countries an HTA assessment can result in a restriction of reimbursability to a specific population. This can also result in a recommendation for non-reimbursement with the consequence that the drug is not introduced in the country (fourth hurdle). These differences can still lead to different consequences being drawn from the EU HTA reports in the future, despite a common „basic report".

Dr Antje Behring *has been working as an adviser at the G-BA office since 2011 and Head of the Medicines Division since June 2020. She has been actively involved in EUnetHTA projects since 2013 and has been chair of the committee responsible for scientific consultations in EUnetHTA 21 (Committee for Scientific Consistency and Quality for Joint scientific consultations, CSCQ JSC) since 2021. From 2009 to 2011 she worked as a consultant pharmacist for the health insurance BARMER in Bavaria. Prior to her pharmaceutical studies and promotion she worked as physiotherapist in inpatient and outpatient care.*

Procedure of the European benefit assessment

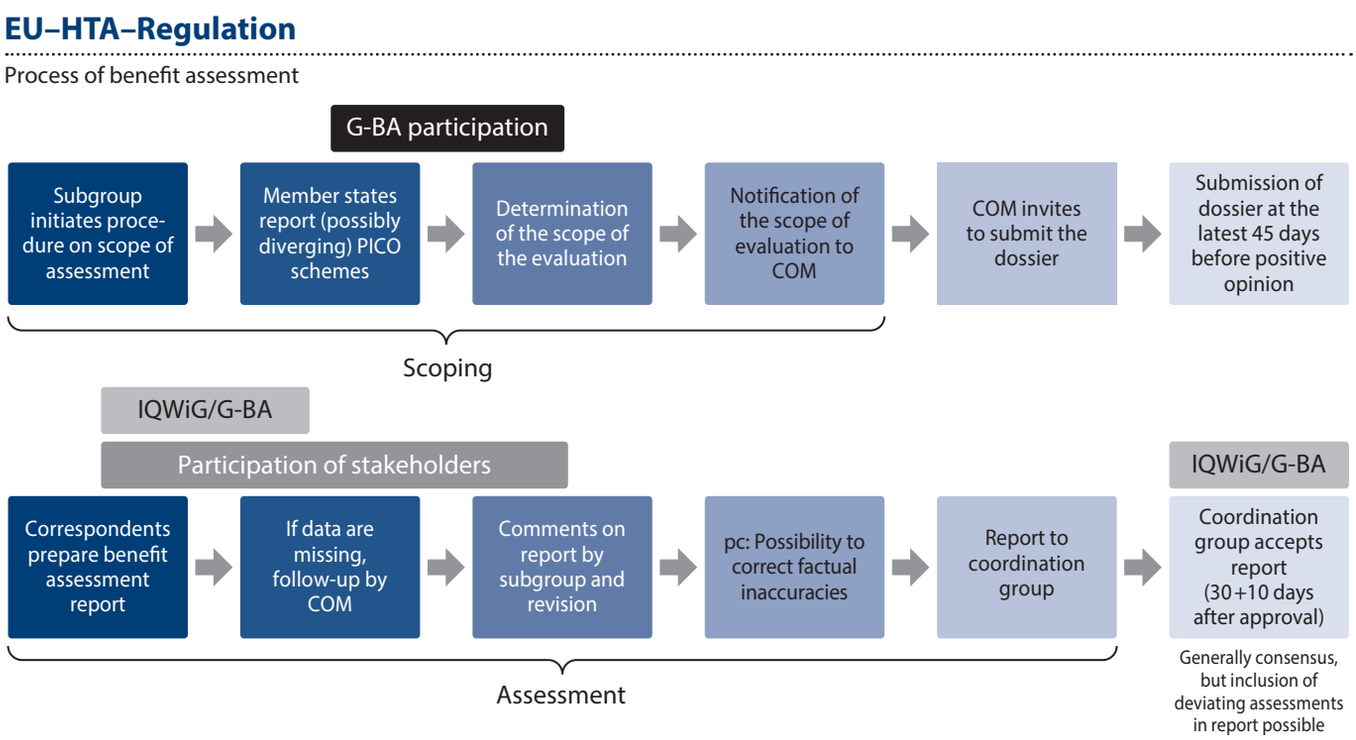
The procedure of the European benefit assessment comprises the following abstract steps:

- Query and consolidation of the assessment scope
- Preparation of the dossier by the pharmaceutical entrepreneur on the basis of the notified scope of assessment and subsequent dossier submission
- Preparation of the draft EU HTA report by the reviewers with the involvement of patients, clinical experts, and other relevant experts
- Approval of the benefit assessment report by the HTA Coordination Group and formal review by the EU Commission.

Without going into the individual steps in detail, some aspects from the experiences in EUnetHTA21 are singled out below and described separately. A number of other procedural steps, such as the involvement of patients at the European level, the handling of conflicts of interest, the precise design of cooperation with the European regulatory authority, the process of joint consultations, or details of the medical device benefit assessment are not considered in this article, although they are also highly relevant.

Challenges in querying the scope of the assessment

The content of the EU HTA report must be designed to satisfy the requirements of the member states. In order to realise this, the HTA regulation stipulates that, in order to determine the scope of the assessment, the respective question for the benefit assessment is submitted by the



Source: Federal Joint Committee

Figure 1: The process of the European benefit assessment is roughly divided into the definition of the scope of the assessment, the preparation of the dossier, the draft EU HTA report, and the approval of the benefit assessment report.

member states before the dossier is prepared. This query follows the PICO scheme: Population, Intervention, Comparator, Outcome. The member states formulate their assessment question according to the relevant population(s) in their country in the therapeutic area, the standard of care to be used as a comparator in the populations, and the commonly accepted endpoints. Germany will participate in the PICO query. Incidentally, this also applies to orphan drugs.

Since the decision to maintain orphan drug status is only made after a positive opinion, an evaluation based on the PICO scheme is required in the event that orphan drug status is withdrawn. If the orphan drug status is retained, there will be no contradiction with the German requirement that pivotal studies be taken into account for orphans, since the assessment of pivotal studies is regularly included in the EU procedure. The preparation of a PICO scheme for the European benefit assessment will represent a new formal step in the early benefit assessment procedure, which has so far been integrated into the consultation procedures according to section 35a SGB V.

In order to prevent the individual questions of the mem-

ber states from flowing unfiltered into a dossier preparation and thus into confusing HTA reports, a consolidation step is interposed between the PICO query in order to precisely work out commonalities and differences of the questions. This specifies for both the dossier creators and the evaluators which evidence is to be prepared and how it is to be subsequently evaluated.

The query and consolidation are described as a so-called scoping process in the regulation. A guideline[2] has already been published in EUnetHTA21, which will be revised on the basis of the experience gained in EUnetHTA21. The development of an understanding of certain formulations, the establishment and application of definitions and terminology, as has been accomplished in the AMNOG in recent years, is still lacking in Europe. For example, in Germany, the term Best Supportive Care (BSC) has been used for years for a conglomerate of different therapies that do not causally address the disease but the (concomitant) symptoms, even if this partly includes active treatment options such as local radiotherapy, surgery, on-demand treatments or similar. BSC varies greatly in terms of the scope of therapy, and the various options are not applied to the same extent for each of the patients covered by the scope. Time for discussion is needed to develop a common interpretation of the terminology in all member states.

Similarly, understanding why some member states require a comparison against active substance A AND B and why any comparison against A OR B is sufficient for other member states. The constellation of „and" or „or" linking of different active ingredients as a comparison needs to be precisely expressed and unambiguously communicated to both pharmaceutical companies and reviewers. The very precise consideration of the therapeutic standard and the active substances to be specifically named as a comparison prior to the HTA evaluation is a challenge for some member states, as this procedure was not familiar before and the HTA evaluation was sometimes focused exclusively on health economic aspects.

Timing and deadlines

The EU HTA regulation specifies only two time points for clinical evaluation reports:

- the latest submission of the dossier 45 days before positive opinion, and
- finalisation of the HTA report no later than 30 days after the approval decision, with an additional 10 days for formal review of the report by the EU Commission.

Even if these key points seem to be fixed, they are flexible upon closer inspection. The timing of the positive opinion for an active ingredient cannot be determined precisely at the start of the approval process, as the duration of the approval process depends on the „clock-stop" periods granted and the type of approval procedure (e.g. accelerated approval). In addition, process durations vary depending on whether the approval is for the first time or for an indication expansion. Similarly unpredictable is the timing of approval following positive opinion. Following a CHMP opinion, the European Commission usually takes a decision after 67 days, which constitutes a legally binding approval.[3] Very often, however, the decision is made more quickly. The varying durations of the approval process will pose a challenge for HTA benefit assessment, as previously planned assessment periods may be shortened and the ability to plan the resources to be deployed will be limited.

The greatest uncertainty remains major changes in the targeted indication in the approval process. Even if the number of major changes in the indication is limited and, according to initial analyses, comes into play in about ten percent of the procedures, these deviations will have a significant impact on the feasibility of the procedure. Exam-

ples of major changes that have an impact on the PICO question of the member states, among others, would be restrictions or extensions of the previously targeted approval population to one or more lines of therapy. In these cases, the pharmaceutical company would have to make different cuts and analyses of the approval population, which cannot be included in the ongoing European benefit assessment procedure. It remains to be seen whether these problems can be solved within the regulations of the EU-HTA-Regulation.

Effects on the German benefit assessment procedure

With optimal implementation of the EU benefit assessment procedure, the European dossier would contain all the necessary data for the early benefit assessment. Then the EU HTA assessment could replace the current dossier assessment by IQWiG or the G-BA for orphan drugs. This would also shorten the duration of the national dossier evaluation. However, there are still uncertainties in the various parameters of the European procedure as to whether this ideal can actually be fully realised. The early benefit assessment in Germany is based on the final approved indication.

Thus, the AMNOG process is aware of contraindications, safety concerns, but also the data gaps already identified by the approval process, which may lead to further data requirements. The European benefit assessment report, which is being prepared in parallel with the approval, carries the risk that the decisions of the regulatory authority, due to lack of knowledge, could not be taken into account and may still require comment at the national level. In addition, it is currently still uncertain which data and analyses will be required from the pharmaceutical company at the European level.

The time to prepare the dossier with different questions will be very limited, even with optimal use of the timelines. In view of the tight timelines, compromises in the data requirements are likely, so that the data package to be submitted in Germany may not be found in its entirety in the data package to be required at the European level, even if the main part will be included. It can therefore be assumed that a small number of analyses (in addition to evaluations of patient numbers and costs) will regularly have to be submitted as supplements for the German process, for example on safety endpoints.

At least at the beginning of the HTA regulation, European and national benefit assessment processes will run in parallel. A differentiation of the data to be submitted for the early benefit assessment depending on whether it is a European procedure (oncological indications) or a national procedure (non-oncological indications) would, in our opinion, contradict the principle of equal treatment. Consequently, all benefit assessments must be based on the same requirements. Since, according to the EU HTA Regulation, a repeated national submission or request of the data submitted at the European level is excluded in any case, the national subsequent requests can only be supplements to the European main part of the analyses.

The European benefit assessment dossier together with the national supplements as well as the European benefit assessment report require an assessment by the IQWiG or the G-BA in order to put the European assessment into the national context. Due to the lack of assessment of the patient relevance of the endpoints in the European procedure, these are to be evaluated in comparison to the procedure practised in Germany to date. In addition, the European methodology to be applied is currently unclear in some areas, so that an assessment of the validity of the methods used, such as for indirect comparisons, would be necessary at national level.

This assessment could then be made available for public comment on the G-BA website, as is the case now.

Another point that may require adjustments in national regulations is the start of benefit assessment procedures in Germany. The European benefit assessment report will not be available until 40 days after the approval decision (including the review by the EU Commission). In Germany, products enter the market relatively quickly, in most cases between 40 and 60 days after approval. If the pharmaceutical is placed on the market in less than 40 days after approval, there would be friction with the submission of the EU HTA report as part of the dossier submission.

The same applies to the requirement that for new indications the dossier must be submitted to the G-BA no later than four weeks after marketing authorization (after 28 days). One could imagine various solutions for this time delay; in addition to legal adjustments, even a subsequent submission of the report would be conceivable.

Essential for the national evaluation will be the European dossier, which is available to the company and, according to current knowledge, also to the member states. Since a double submission of data is not allowed, a reference to the European dossier and the evaluations stored there must be possible in the national dossier templates; at best, a bilingualism of the module templates should be aimed at in order to facilitate the comparison with the requirements.

Conclusion

Despite the greatest efforts of the HTA agencies in the various European HTA projects, ambiguities and differences remain even 1.5 years before the introduction of the EU HTA procedure, due to different healthcare systems and pricing mechanisms in the member states. Until the ambiguities in methodology and requirements are resolved, the impact on the German AMNOG procedure cannot yet be definitively assessed.

However, it is foreseeable that a new procedural step will have to be introduced in order to be able to perform the query of the assessment scope of the member states. It also seems uncertain from today's perspective whether all evaluations required at national level will be available at the European level. It remains to be seen in the procedure which additional analyses remain necessary for the national procedure. Furthermore, it remains to be seen what uncertainties the European benefit assessment, which is to be prepared in parallel with the approval process, will entail, since it was prepared in ignorance of the approval decisions. In addition, it must be clarified how the start of the evaluation in Germany is to be structured if the EU HTA report is not yet available and to what extent the EU HTA will have an impact on the orphan privilege.

Despite all questions and the current impression of an elaborate, additionally complex procedure from the German point of view: From a European perspective, the central dossier and the central HTA report offer added value for many states that have not yet established an evaluation system or only unsystematically submit products to an evaluation. A centralised procedure reduces the flexibility of companies to focus differently on their product in different countries. The process becomes more illustrative for all of Europe through central processing, as the underlying, complete data, evidence, and corresponding analyses are available and public to all. This alone has an added value for Europe.

References

[1] EUnetHTA JA 2, 2018, An analysis of HTA and reimbursement procedures in EUnetHTA partner countries: final report online: https://go.sn.pub/MKDAeR [zuletzt abgerufen am 24.4. 2023]

[2] EUnetHTA 21, 2022, Practical Guideline D4.2 Scoping Process, online: https://go.sn.pub/qL56lp [zuletzt abgerufen am 24.4. 2023]

[3] EMA, 2020, EMA/587373/2021, Guide to information on human medicines evaluated by EMA
What the Agency publishes and when; online: https://go.sn.pub/nxtuAE [zuletzt abgerufen am 24.4. 2023]

Early scientific advice and cooperation in the context of the EU HTA process

Bettina Ziegele | Paul-Ehrlich-Institut, Langen, Germany

The focus of the HTA Regulation is the cooperation between regulation of pharmaceuticals and HTA in the clinical evaluation of pharmaceuticals and medical devices. In Germany, there is a regular exchange between the national institutions, the higher federal authorities, and the Federal Joint Committee (G-BA) regarding the benefit assessment of pharmaceuticals. One pillar is consultations on the early identification of requirements for clinical studies. In the Simultaneous National Scientific Advice (SNSA), pharmaceutical authorities from several member states jointly advise applicants with the aim of harmonising their requirements, particularly regarding clinical studies.

Introduction

With the HTA Regulation, benefit assessment of pharmaceuticals and medical devices – that has been conducted exclusively at national level so far – will be replaced by a joint HTA assessment of the member states at European level. These new legal European framework conditions require a number of adjustments at various levels and in different areas: To ensure that the procedure meets the new legal requirements, established national procedures must be adapted on the one hand, and new processes must be introduced on the way to a joint benefit assessment on the other.

However, the changes that are required do not only relate to the cooperation of the individual national HTA institutions. The regulation also provides for the cooperation of institutions from pharmaceutical regulation and benefit assessment based on joint clinical evaluations. Consequently, the benefit assessment procedure not only requires agreement between the HTA institutions of the member states, but also involves vertical coordination of requirements between experts from pharmaceutical regulation and HTA experts. Accordingly, requirements from both branches of regulation are placed on data from clinical studies, so that harmonisation does not only take place in the context of individual national HTA assessments but is also reflected in the regulatory context of the approval of pharmaceuticals.

These challenges can be met at the vertical level with the coordination of requirements between regulation and benefit assessment and at the horizontal level through interaction between member states – both as early as possible. The cooperation between higher federal authorities and G-BA in Germany can be cited as an example of early, efficient, and purposeful cooperation between the two regulatory areas.

In the area of pharmaceutical regulation, an early and

direct exchange between the member states is already possible at multinational European level and with particular reference to Regulation (EU) No 536/2014: Here, with the simultaneous participation of several National Competent Authorities (NCAs), a new format for early and broad consultation is available to applicants with a focus on the planning and preparation of clinical studies in a pilot project.

The aim of this new consultation format is to harmonise various positions and requirements as far as possible while at the same time identifying possible existing differences between the participating member states. Against this background, the consistency of the consultation results can make a significant contribution to supporting the design of multinational clinical studies in the European framework and simplifying the process of the approval procedure for clinical studies for both sides, so that innovative developments in particular can find their way to patients more quickly.

Bettina Ziegele *is the Liaison Officer at the Paul Ehrlich Institute responsible for national stakeholder cooperation and international affairs. After setting up and managing the Innovation Office, she worked at the Federal Ministry for Health (BMG). She then familiarised herself with the formal and content-related requirements of benefit assessments at the G-BA. Bettina Ziegele has been a member of the EU Innovation Network at the EMA for many years and heads the working group on the Simultaneous National Scientific Advice (SNSA) pilot project based there. She holds a Master's degree in economics and linguistics from the University of Heidelberg.*

Focus on the development of innovative pharmaceuticals

As the federal institute for vaccines and biomedical pharmaceuticals, the Paul Ehrlich Institute (PEI) is responsible for sera, vaccines, blood preparations, tissues and tissue preparations, allergens as well as advanced therapy medicinal products (ATMPs) with the subgroups gene therapeutics, somatic cell therapeutics and biotechnologically processed tissue products, xenogeneic pharmaceuticals, and genetically engineered blood components.[1] Thus, the PEI is not only responsible for traditional pharmaceuticals, such as conventional vaccines, but also focuses on innovative pharmaceutical developments, of which the group of ATMPs is considered separately. There are separate legal regulations for ATMPs at European and national level, which consider the complexity and the innovation potential of these developments.[2]

In the healthcare context, the relevance of innovative pharmaceuticals is also reflected in the form of new regulations in the relevant legislation. New framework conditions are being created for quality requirements on the use and benefit assessment of innovative pharmaceuticals, and thus new standards are being established for cooperation between HTA and the higher federal authorities. Since ATMPs receive special attention in this legal context, the cooperation between the G-BA and the PEI is intensifying, particularly in this area, in both qualitative and quantitative terms.[3]

Cooperation between PEI and G-BA

The cooperation between the PEI and the G-BA is based on the legal regulations of Section 35a and Section 136 a SGB V[4] and consists of two pillars: One pillar is the participation of the higher federal authorities in decisions of the G-BA and the second pillar is joint consultations from both branches of regulation.

Participation of the higher federal authorities in G-BA measures

The pillar of cooperation between the higher federal authorities and the G-BA has been legally stipulated with the Act for Greater Safety in the Provision of Pharmaceuticals (GSAV) in 2019 and regulates the participation of the higher federal authorities prior to the adoption of decisions by the G-BA.[5] The measures serve the purpose of safety of innovative or complex pharmaceuticals that are urgently needed for the care of patients and are reflected in the following two statutory regulations:

a.) Section 136 a SGB V[6] regulates measures to ensure quality in the use of advanced therapy medicinal products (ATMPs). And the cooperation here provides for consultation with the PEI, based on the special regulatory requirements for these pharmaceuticals due to their complexity and special technical features within the framework of the approval of pharmaceutical products. The cooperation with the PEI also includes the regular exchange of information on new developments and decisions that affect the use of ATMPs.

Thus it is possible that the G-BA is informed about new developments at an early stage and can take them into account, which gives it sufficient time to develop appropriate quality assurance measures for the use of ATMPs. The quality assurance measures are thus of outstanding importance regarding patient safety, as they ensure the appropriate use of a pharmaceutical, both in the outpatient and inpatient sector.

b.) Section 35a para 3b SGB V[7] regulates the post-market data collection and evaluation for the benefit assessment of pharmaceuticals for which complete data for the assessment of benefit or additional benefit are not yet available upon approval, but which are urgently needed for the care of patients. For these pharmaceuticals with either conditional approval or approval under exceptional circumstances according to Article 14(7) or (8) of Regulation (EU) No. 726/2004, as well as for approvals of pharmaceuticals for the treatment of rare diseases according to Regulation (EU) No. 141/2000, the G-BA can request post-market data collection and evaluation from the pharmaceutical company for the purpose of benefit assessment. In 2020, the GKV-FKG (Fairer Health Insurance Competition Act) also defined in more detail that the G-BA can already request post-market collection and evaluation when the pharmaceutical is placed on the market.[8]

The requirements for the duration, type, and scope of data collection, including the formats to be used, are determined by the G-BA. BfArM or PEI must be involved before issuing a decision on such a measure. The involvement of the competent higher federal authority is against the background of coordinating the post-market data collections of the G-BA with any approval-related requirements and conditions. In this context, current and planned data collections on the pharmaceutical must be considered, in particular those resulting from requirements or other ancillary provisions of the authorisation or approval authorities. The aim of post-market data collection and evaluation for the purpose of the benefit assessment by the G-BA is to supplement the existing database of clinical data already available and to be able to make these pharmaceuticals available to patients in the statutory health insurance as

quickly as possible due to the particular need for the treatment.[9]

Consultation services in the context of requirements from pharmaceutical regulation and HTA

The implementation of joint consultations is regulated in Section 35 a (7) SGB V[10] and provides for consultations of applicants at the G-BA before the start of phase III registration studies, for the planning of clinical studies or for post-market data collection with the participation of the BfArM or PEI. The aim is to enable close coordination and planning of the requirements both regarding the approval and benefit assessment in an early consultation with the participation of the higher federal authority.

In these consultations, the determination of the (appropriate) comparative therapy plays a special role, so that e.g. questions regarding the standard of care, evidence base and healthcare practice are at the forefront of the discussion. The participation of the PEI ensures the appropriate consideration of the requirements that are necessary from the perspective of pharmaceutical regulation. The G-BA plays a key role in this procedure, so it is the addressee for consultation requests, prepares the protocol and collects the fees within the framework of Section 35a (7) SGB V[11].

The option of joint consultations was supplemented by joint advice in 2016: This format was defined in an agreement on structured cooperation between the G-BA, BfArM and PEI and enables the application for Scientific Advice at the higher federal authority with the participation of the G-BA.[12] The aim of this consultation format is to achieve a close and structured exchange as early as possible on common questions regarding the approval of pharmaceuticals on the one hand and the early benefit assessment of pharmaceuticals on the other.

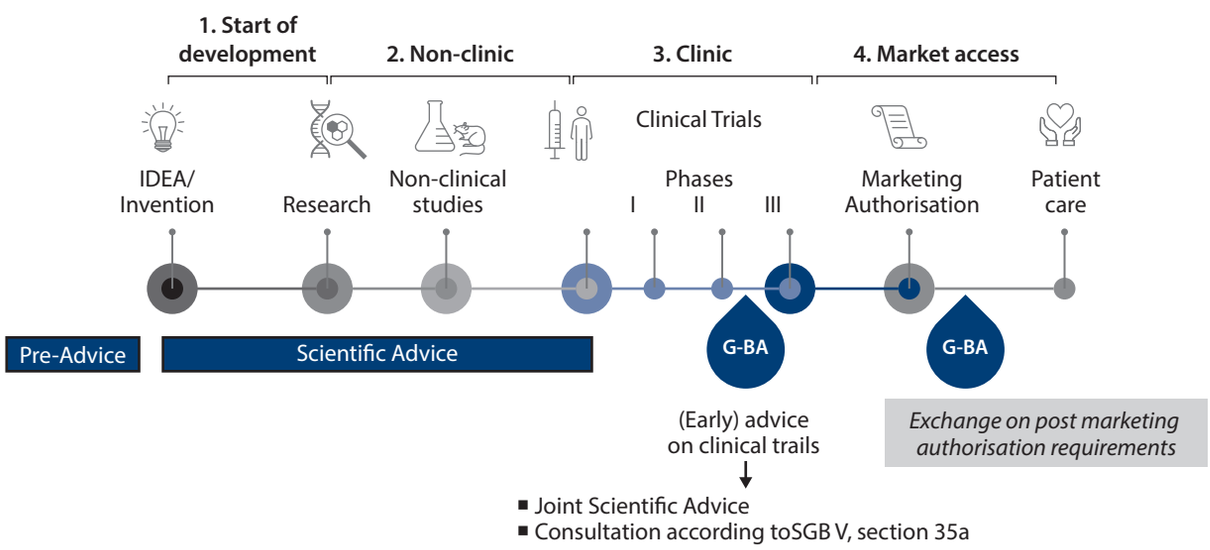
The focus here is on the question of how sufficient evidence can be generated within the framework of the implementation of studies on clinical pharmaceuticals both for the assessment of the regulatory issues (approval) and for the assessment of the issues relating to social insurance issues (early benefit assessment). The higher federal authority, i.e. PEI or BfArM, are in charge of this consultation format, so that they are the recipients of the consultation applications and are responsible for the preparation of the protocol and the charging of fees.

This means that two options are available for joint consultation on the planning of clinical studies for questions relating to approval and benefit assessment. It should be noted that neither of these formats can fully compensate for the other, as the focus is different: In case of joint advice, the focus is on scientific regulatory issues, the discussion of which is supplemented by an initial assessment of the requirements from the area of benefit assessment by experts from the G-BA's office.

This format can thus not be equated with a G-BA's advisory procedure according to Section 35a SGB V with committee participation. Nevertheless, e.g. the first format can be used before the second. The guideline on mutual participation in consultations at the G-BA and the BfArM or PEI provides information on the rationale, objectives, application, and procedure of these two consultation options.[13]

Moreover, there is also the possibility of joint consultations to plan the requirements of post-market data collection for the benefit assessment at an early stage and coordinate them with the approval-related requirements. The legal basis in Section 35 a (7) SGB V was expanded to include consultations on post-market data collection with the participation of the higher federal authority.[14] In principle, the requirements can also be addressed from both regulatory areas prior to approval or coordinate them as early as possible (figure 1).

Scientific Advice along the product life cycle



Source: Paul-Ehrlich-Institut – Bettina Ziegele

Figure 1: Consultation formats in parallel with development pave the way for the identification of requirements at an early stage in preparation for joint consultation on the planning of clinical studies, approval, and benefit assessment.

The available consultation formats parallel with development thus pave the way at an early stage for the identification of requirements in preparation for joint consultation on the planning of clinical studies, approval, and subsequent benefit assessment – also regarding post-market data collection. In the further course of clinical development, joint Scientific Advice and consultations based on Section 35a of the German Social Code, Book V are available for the design not only of phase III registration studies, but also of early phases of clinical studies, with a special focus on the data to be generated later. The background is that phase II studies can also form the basis for the application for a conditional approval or approval under exceptional circumstances. Accordingly, conditions for post-market data collection can already be imposed when the approval is granted for the acquisition of further data on safety and efficacy within the framework of post-marketing safety (PASS studies) or post-marketing efficacy data (PAES studies)[15]

Thus, the possibilities of joint consultation are an important tool to bring content-related and structural requirements for joint data collection based on the collection of real word data in the broadest sense as far as possible to a common denominator and develop a best-practice concept so that data that is difficult to generate, especially e.g. in case of rare diseases, can be collected as efficiently as possible and used as effectively as possible for the objectives of both regulatory areas.

Consultations in comparison

A comparison of the various advisory formats on innovative pharmaceuticals using the example of ATMPs and monoclonal antibodies (MAK) for the years from 2019 to 2022 shows a very heterogeneous picture: In case of monoclonal antibodies, the number of Section 35a SGB V consultations of the G-BA per year was almost twice as high as the Scientific Advice consultations of the PEI. However, for both formats, the number of consultations almost doubled to eventually level off at 75 % of the previous maximum values. In case of ATMPs, the Scientific Advice consultations were several times higher than the G-BA consultations. An examination of the PEI's participation in the G-BA consultations reveals a clear result: For MAK, the PEI participated in an average of 15% of the G-BA consultations. For ATMPs, after a slight increase in participation from 9.5 to 12%, the PEI has no longer participated in any G-BA consultations in the last two years (figure 2).

In the overall view, the G-BA consultations across all pharmaceuticals remain relatively constant with a number between 228 and 294 consultations during the evaluation period. The number of G-BA consultations on pharmaceuticals for which the PEI is responsible, on the other hand, fluctuates between 72 and 142 during this period and even decreases by almost half in the opposite direction to the total number of G-BA consultations. The PEI's participation in these consultations, on the other hand, increases slightly to 30% and then returns to the previous year's value of 11%. It is noticeable that in 2020, with a 50% lower share of pharmaceuticals under PEI responsibility, the PEI's participation in these consultations was 30%. An analysis of the joint consultations within the framework of Joint Advice is not necessary, as the number of consultations conducted in this format is too low.

Within the framework of the HTA regulation (Regulation (EU) 2021/2282), the first joint clinical evaluations of new pharmaceuticals are to begin as early as January 2025. Most important are innovative pharmaceuticals such as ATMPs and oncology products, including those for rare diseases.[16] The relevance of the assessment of these pharmaceuticals becomes clear when looking at some figures on the development and current status of this group of pharmaceuticals using the example of the pharmaceuticals for which the PEI is responsible. A comparison of the consultations of the Federal Joint Committee based on Section 35a SGB V on ATMPs with approvals granted for ATMPs shows that over the course of time, two consultations (in 2019) and seven consultations (in 2020) are offset by three or one approval(s) of ATMPs in 2020 and 2021, respectively, and five in 2022.

The retrospective analysis of the overall development of the central procedures in the area of responsibility of the PEI for the years 2017-2022 shows that the PEI has taken over by far the most procedures in the role of rapporteur and peer reviewer and also occupies a position in the upper third of all participating member states in the number of co-rapporteurships. Prospectively, this development will tend to continue in the assumption of 24 (co-)rapporteurships with 15 procedures in the area of MAK and 5 in ATMP and 4 in vaccines.

The PEI's participation in procedures within the framework of pharmaceutical monitoring at the level of the Pharmacovigilance Risk Assessment Committee (PRAC) shows similar figures: In the same period, the PEI took over between 23 and 55% of the total (co-)rapporteurships and received more procedures than applications. Particularly in case of applications for approval of clinical studies of biomedical pharmaceuticals, the figures at the pan-European level indicate a clear upward trend regarding the development of innovative pharmaceuticals: The annual number

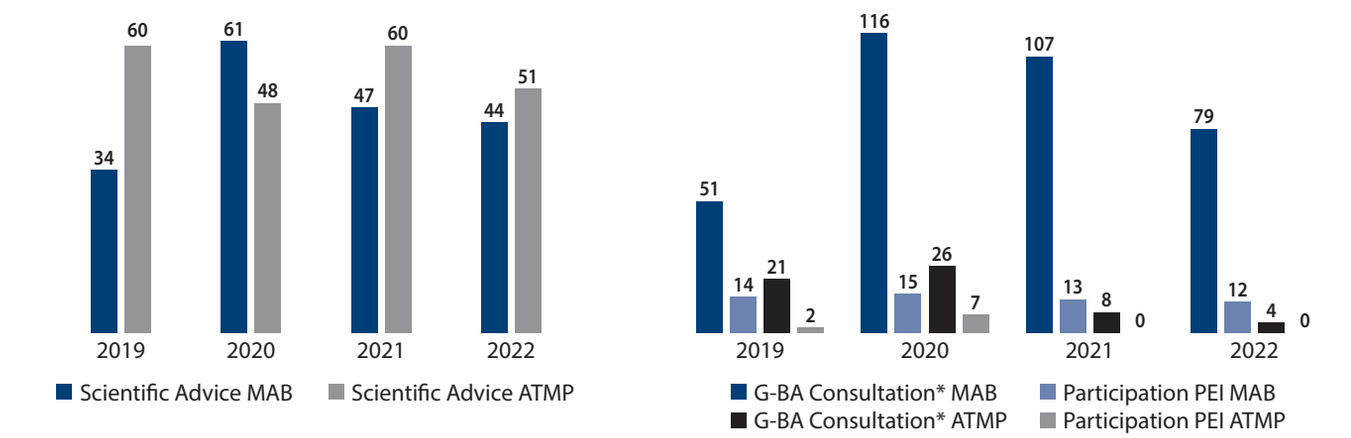


Figure 2: For MAK, the PEI participated in an average of 15% of the G-BA consultations. For ATMPs, after a temporary increase in participation, the PEI has most recently not taken part in any G-BA consultations.

of clinical studies of biomedical pharmaceuticals has increased from 153 to 401 between 2005 and 2022, of which 75 procedures were applied for under the new European Regulation (EU) No 536/2014 (CTR).[17]

Conclusion and outlook

Technological progress, digitalisation and, in particular, the possibilities of genetic engineering are reflected in the numbers of corresponding applications for clinical studies in recent years, as well as in the increased number of approvals of ATMPs. The development of highly complex and innovative pharmaceuticals for small populations with a high medical need, such as rare diseases, but also therapeutic approaches for the treatment of common diseases, not only sets completely new standards for the conception, design, approval, and implementation of clinical studies.

The options of market access in the context of conditional approval or approval under exceptional circumstances as well as for pharmaceuticals for the treatment of rare diseases based on limited clinical data on safety and efficacy from e.g. phase II clinical studies usually require post-market data collection to generate further data on the safety or efficacy of these pharmaceuticals in the form of post-authorisation safety (PASS) or post-authorisation efficacy studies (PAES). Since the data obtained in the context of the clinical studies may also be considered insufficient for the benefit assessment, the AMNOG also faces the challenge of striking a new balance between innovation and affordability of pharmaceuticals in the context of providing patients with these urgently needed pharmaceuticals.

The existing medical need and opportunities for academic and/or industrial research to develop innovative and complex pharmaceuticals presents the same challenges to

both regulatory areas in their aim to improve patient care. The requirements for generating (additional) clinical data can form a common starting point for designing the legally given framework in such a way that the development of pharmaceuticals and healthcare can be understood as a learning cycle with the participation of all stakeholders, such as academia and industry as well as regulatory and HTA institutions, but also ethics committees and patient representatives.

To efficiently use the limited resources available in the various fields and provide patients with optimised access to safe, effective, and beneficial pharmaceuticals and therapies throughout Europe, it is necessary to promote the cooperation of all stakeholders in a needs-oriented and purposeful manner (figure 3).

The HTA regulation provides the legal framework for this. The focus is on how the interaction of the stakeholders can be optimised to support the process from bench to bedside in such a way that a sustainable and stable balance between the development of innovations and their application to patients is achieved. As already stated, there is great potential in the development of innovative pharmaceuticals and increasingly available procedures in the area of regulation of Scientific Advice to applications for clinical studies to approvals confirm this trend.

As a result, we can continue to expect increasing demand for Scientific Advice. In particular, the trend towards conducting clinical studies in early phases and with a smaller number of cases instead of the previous „gold standard" of large randomised and double-blind pivotal phase III studies as the basis for approval – especially for conditional approvals – confirms the increasing demand for advice regarding clinical studies. An increasing demand is also induced because consultations are increasingly used to clarify questions in the run-up to the submission of applications for clinical studies and to avoid queries in the ongoing approval procedure, which is very limited in time.

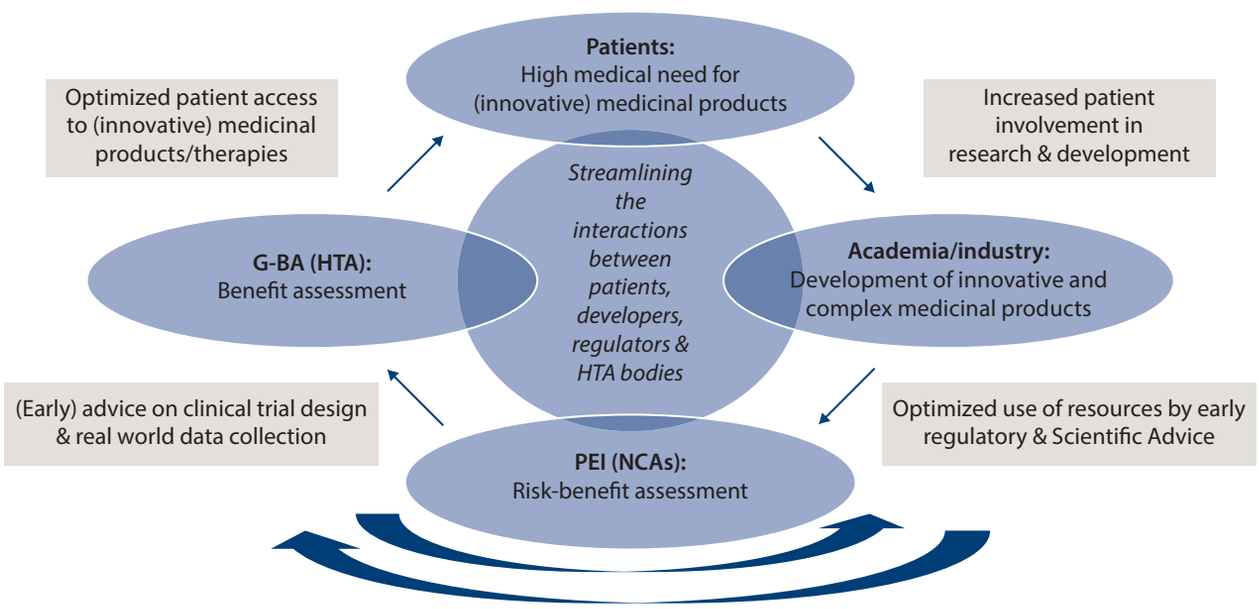
Against the background of the consultation figures presented, it becomes clear that, on the one hand, the number of Scientific Advice consultations for relevant innovative pharmaceuticals is not reflected in joint section 35a consultations, but on the other hand, an increasing number of joint section 35a consultations for ATMPs in the run-up seems to correlate with increasing approvals in subsequent periods. Moreover, in the totality of the figures considered, a large number of G-BA consultations without PEI participation for relevant innovative pharmaceuticals such as MAK contrast with a high number of PEI participations in procedures on the way to possible approvals. Post-market data collection from both regulatory areas can be imposed on these approvals that are granted access to the market under the above-mentioned special conditions.

Regarding the EU HTA Regulation, the German Association of Research-based Pharmaceutical Companies (VFA) calls for joint scientific consultations to coordinate the requirements of the member states and with a view to maximising the common benefits of clinical studies.[18] In a pilot project, the EU Innovation Network (EU-IN)[19] has implemented a format that complements the EMA's Scientific Advice by enabling multinational consultations for the early coordination of clinical studies requirements with a current focus on regulatory issues

Simultaneous National Scientific Advice (SNSA)20

The SNSA consultation format was designed to optimise early consultation with a focus on the planning of clinical studies. The SNSA enables consultation with the simultaneous participation of several regulatory medicines agencies from different member states as part of a pilot project and is particularly designed to promote the development

Prerequisites and opportunities for the development of innovative pharmaceuticals



Source: Paul-Ehrlich-Institut – Bettina Ziegele

Figure 3: To make efficient use of the limited resources available, it is necessary to continuously organise the cooperation of all stakeholders in a demand-oriented and target-oriented manner.

of innovative pharmaceuticals. The aim of the concept is to establish a more efficient procedure for consultations at several NCAs compared to individual national Scientific Advice at the respective NCAs, while optimising the resources of both sides.

Upon a closer look, the project is designed to promote the exchange of experts between the NCAs, but also to strengthen interaction at the European level or directly with the EMA. Regarding the applicants, the aim is to be able to find out the positions of several NCAs in only one Scientific Advice procedure and to achieve the greatest possible agreement among the participating NCAs regarding the requirements.

In the current second pilot phase, the procedure is being optimised regarding the coordination and participation of the 17 NCAs so far. In this extended phase, up to three NCAs can be actively involved in each consultation and, in addition, another NCA can participate as an observer. In justified cases, the SNSA can also take place with more than three NCAs, e.g. considering NCAs relevant to the clinical studies. In addition, there is also the possibility of involving other relevant stakeholders, such as representatives of the Clinical Trials Facilitation Group (CTCG) or ethics committees. The result of the consultation is summarised in a consolidated meeting protocol that reflects the positions of the individual actively involved NCAs. Fees are char-

ged based on the national cost regulations of the individual actively involved NCAs.

The optimisation of the procedure includes a standardised application form, an overview of the timeline of the procedure as well as updated guides for applicants and involved parties, a list with a fee overview of the different NCAs and, finally, the establishment of a platform to make the interaction between applicants, project coordinators and NCAs more efficient.

Most of the 41 SNSA procedures conducted so far have been for ATMP and MAK, followed by COVID-19 vaccines and other mostly new vaccine approaches. The focus is thus on novel developments and confirms the relevance of this consultation format for innovative pharmaceuticals in particular. In terms of indications, the focus was on infectious diseases as well as COVID-19 diseases, but also developments in the oncological and neurodegenerative fields. The evaluation after the first pilot phase also concludes that another important project goal was achieved: Especially in the area of (predominant) clinical questions, the positions of the NCAs were convergent.

But also in the positions on quality and non-clinical requirements, no major divergences were found. Another result of this evaluation points to the fact that from approx. 50% of the consultations with the involvement of the applicants, topics could be identified which, either due to new regulatory aspects or their general regulatory importance, were elevated to the European level for further discussion or pursued in EMA working groups.

In summary, the SNSA concept offers the possibility of tailored early and sustained consultations involving broad regulatory expertise across EU member states. The concept aims to avoid significant differences in the positions of the represented NCAs and identify concurring but, if necessary, differing opinions at an early stage, as well as to complement crucial topics for further discussion at HMA or EMA level, e.g. CTCG or the Scientific Advice Working Party (SAWP).

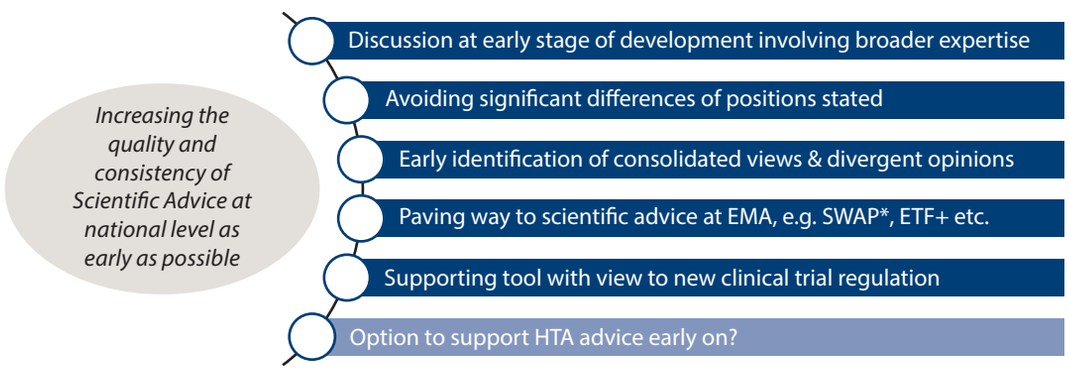
With its focus on innovative developments and special attention to initial clinical applications, the SNSA is considered a valuable tool for the planning and design of clinical studies in preparation for the application within the framework of the CTR (Regulation (EU) No. 536/2014). The conceptual spectrum of early involvement of other stakeholders, above all the ethics committees, creates the opportunity to establish a platform that also provides space for future discussions of complementary relevant clinical questions for application in patients and the decisive prerequisites for the introduction of innovative pharmaceuticals into regular patient care (figure 4).

Finally, the overarching goal of the SNSA is to promote the exchange of knowledge between all stakeholders in the course of sustainably improving the support of innovative developments throughout the entire life cycle and thus sustainably strengthening regulatory science and research. A goal that will have to be further defined soon by the special requirements within the framework of HTA regulation with the intensification of the cooperation between regulation and benefit assessment.

Disclaimer

The views expressed in this presentation are the views of the author. Decisions are made while considering individual cases on scientific grounds. Neither the Paul-Ehrlich-Institut nor its experts obtain any finances from industry developing pharmaceuticals. Research at the Paul-Ehrlich-Institut is financed by public money including peer-reviewed research grants.

Simultaneuous National Scientific Advice: Procedures for more efficient advice



*SAWP: Scientific Advice Working Party; +ETF: Emergency Task Force

Source: Paul-Ehrlich-Institut – Bettina Ziegele

Figure 4: The SNSA concept offers the possibility of tailored early and sustainable consultations involving broad regulatory expertise across EU member states.

References

[1] § 77 German Medicinal Products Act (Arzneimittelgesetz (AMG)

[2] Regulation (EC) No. 1394/2007

[3] https://www.bundesgesundheitsministerium.de/gsav.html

[4] https://www.sozialgesetzbuch-sgb.de/sgbv/1.html

[5] https://go.sn.pub/8lY6XB

[6] https://www.sozialgesetzbuch-sgb.de/sgbv/1.html

[7] https://www.sozialgesetzbuch-sgb.de/sgbv/1.html

[8] https://go.sn.pub/IpQtl

[9] https://www.g-ba.de/themen/arzneimittel/arzneimittel-richtlinie-anlagen/anwendungsbegleitende-datenerhebung/

[10] https://www.sozialgesetzbuch-sgb.de/sgbv/1.html

[11] https://www.sozialgesetzbuch-sgb.de/sgbv/1.html

[12] https://www.pei.de/SharedDocs/Downloads/DE/newsroom/pm/anhang-pm-0-9-2016-strukturierte-zusammenarbeit-gba-bfarm-pei.pdf?__blob=publicationFile&v=2

[13] https://www.pei.de/SharedDocs/Downloads/DE/regulation/beratung/leitfaden-geratung-bfarm-gba-pei.pdf?__blob=publicationFile&v=2

[14] https://www.sozialgesetzbuch-sgb.de/sgbv/1.html

[15] https://go.sn.pub/u5O5kt

[16] https://go.sn.pub/4Vk6rh

[17] Source: PEI

[18] https://www.vfa.de/de/wirtschaft-politik/eu-hta-verordnung

[19] https://www.hma.eu/about-hma/working-groups/eu-innovation-network-eu-in/eu-innovation-network-eu-in.html

[20] https://www.hma.eu/about-hma/working-groups/eu-innovation-network-eu-in/eu-innovation-network-eu-in.html

Challenges in market access for pharmaceuticals in the context of the EU HTA Regulation

Professor Luca Pani | University of Modena and Reggio Emilia, Italy; University of Miami, USA

The European Union (EU) Joint Clinical Assessment (JCA) regulation has been developed, inter alia, to address market access hurdles by unifying health technology assessment (HTA) procedures among EU member states. This paper explores the characteristics of the JCA regulation, its potential influence on market entry for groundbreaking pharmaceuticals, and the necessity of employing adaptive models incorporating real-world evidence and innovative pricing schemes.

As the field of specialised therapeutics expands with advanced therapy medicinal products (ATMPs) and innovative treatments targeting small populations, current HTA frameworks face significant challenges in adapting to these advancements. We explore the issues surrounding reimbursement and emphasise the need for adaptive models that consider real-world evidence.

Introduction

The European Union's (EU) new Health Technology Assessment (HTA) Joint Clinical Assessment (JCA) Regulation underscores the potential and challenge posed by innovative treatments.[11] Current HTA and reimbursement models are inadequately prepared to accommodate the surge of novel therapies, necessitating innovative management and entry agreements. With an estimated 932 cell and gene therapies currently in the development phase and approximately 39 expected approvals by 2022,[2] the demand for more appropriate reimbursement models and sustainable payment terms are urgently needed.

The emergence of new treatments, including cell and gene therapies, has posed significant challenges to the EU HTA JCA Regulation on the Joint Assessment of Medicinal Products. The existing set of values is proving insufficient for assessing and reimbursing these breakthrough treatments.

The traditional HTA process primarily focuses on traditional therapies, such as small molecule pharmaceuticals and antibodies. However, it may not be appropriate for specialised therapeutics targeting small populations, such as advanced therapy medicinal products (ATMPs) or highly innovative treatments.[15] This paper explores the challenges of evaluating specialised therapeutics, presents case studies of affordability inconsistencies, and proposes possible solutions for developing adaptive reimbursement models that take into account real-world evidence.

The rapidly evolving landscape of innovative pharmaceuticals, including cell and gene therapies, has the potential to revolutionise healthcare by providing targeted and personalised treatments for previously untreatable diseases.[7] However, the emergence of these novel therapies has shown that the existing Health Technology Assessment (HTA) framework is reaching its limits, leading to market access problems.

The European Union (EU) Joint Clinical Assessment (JCA) Regulation aims to remove these barriers by streamlining the HTA process across member states, promoting transparency, and facilitating collaboration between regulators and payers.[11]

Challenges in assessing specialised therapeutics

The traditional HTA process, designed primarily for conventional therapies such as small molecule pharmaceuticals and antibodies, has difficulty considering specialised therapeutics that target niche populations or highly innovative treatments. Rigid decision-making criteria and shortened development times for Advanced Therapy Medicinal Products (ATMPs) often result in insufficient evidence of their efficacy and durability of response.[18,16] Moreover, in the current environment there is a lack of appropriate reimbursement models and sustainable payment terms for the management of marketing authorisation contracts.[22,19]

The push for pharmaceutical innovations has outpaced progress in HTA processes and negotiation strategies. For example, despite pan-European approval, the AMTP Chondro Celect® could only obtain reimbursement in three European countries, which ultimately led to the withdrawal of the product.[24] Similarly, Glybera® (alipogene tiparvovec) was administered to just one patient outside of clinical trials due to its prohibitive price of $1 million, which led to its withdrawal from the market in 2017.[14]

Several strategies have been proposed to overcome these challenges, including the use of adaptive pathways,9 the incorporation of real-world evidence into decision-making,[25] and the development of innovative pricing models, such as value-based pricing and performance-based risk-sharing agreements.[16] Using these approaches, HTA frameworks can better address the unique characteristics of specialised therapeutics, ultimately leading to better patient access and better healthcare outcomes.

The current state of HTA and reimbursement models is inappropriate for the rapidly growing field of novel therapies, necessitating the development of new management and approval arrangements. By addressing the challenges in evaluating specialised therapeutics and introducing adaptive reimbursement models that take into account real-world evidence, the EU can foster an environment that supports the successful integration of innovative therapies into healthcare systems, ultimately benefiting patients and healthcare outcomes.

Features of the new EU JCA regulation

The new EU Joint Clinical Assessment (JCA) regulation presents several key features aimed at enhancing the Health Technology Assessment (HTA) process for innovative phar-

Professor Luca Pani, *is Professor of Pharmacology at the University of Modena and Reggio Emilia in Italy and Professor of Clinical Psychiatry at the University of Miami, USA. He has been Director General of the Italian Medicines Agency (AIFA) from 2011 to 2016. He was also a member of the Committee for Medicinal Products for Human Use (CHMP) and the Scientific Advice Working Party (SAWP) at the EMA in London from 2010 to 2017. Moreover, he chaired the EU Telematics Committee from 2013-2016.*

maceuticals and, in particular, addressing the challenges associated with specialised therapeutics.[11]

1. Joint clinical assessments: The regulation establishes a centralised process for conducting joint clinical assessments of new health technologies, including innovative pharmaceuticals, to ensure consistency and reduce duplicative efforts across member states.[20]

2. Early dialogue: The regulation promotes early dialogue between manufacturers, HTA bodies and regulators, facilitating the development of robust evidence packages that meet the needs of all stakeholders.[27]

3. Enhanced collaboration: The regulation promotes collaboration between member states and enables the sharing of expertise and resources to improve the quality and efficiency of HTAs.[23]

4. Voluntary cooperation: The regulation allows member states to cooperate voluntarily on HTAs for specific health technologies and provides an opportunity to pool resources and share best practices.[3]

By implementing these features, the EU JCA regulation aims to create a more harmonised and efficient HTA environment that is better equipped to assess and evaluate innovative pharmaceuticals, including specialised therapeutics like cell and gene therapies.

EU JCA in addressing market access challenges

The new EU JCA regulation has the potential to address market access challenges for innovative pharmaceuticals in several ways:[11]

1. Harmonisation: By harmonising the HTA process across member states, the JCA regulation reduces the administrative burden for manufacturers and speeds up market access for innovative pharmaceuticals.[28]

2. Improved evidence generation: The early dialogue feature enables manufacturers to gain a better understanding of the evidence requirements that regulators and payers have, ensuring that clinical study designs and data collection strategies are consistent with the needs of all stakeholders.[15]

3. Enhanced transparency: The JCA regulation promotes transparency by mandating the availability of joint clinical assessments to the public and enabling stakeholders to better understand the rationale behind HTA decisions and reimbursement decisions.[17]

4. Faster decision-making: By promoting cooperation between member states and facilitating the sharing of expertise and resources, the JCA regulation may lead to faster decision-making and improved market access for innovative pharmaceuticals.[26]

Reducing uncertainty and enhancing management entry agreements (MEAs):

To address these concerns more effectively, study designs should be developed to gather evidence for both the pharmaceutical and the associated biomarker test(s).[8] Product sponsors should prepare for the development of biomarker test(s) that are useful for regulators and payers.[15] Moreover, the strength of evidence supporting biomarkers should inform reimbursement criteria, and the identification and management of micro-heterogeneity leading to combined therapies should be supported by adaptive reimbursement schemes.[1]

Progressive imbursement models and real-world evidence

The concept of „avoidable costs“ illustrates that highly effective therapies can enhance efficiency by reducing hospital treatments. However, these efficiency gains are rarely demonstrated in short-term clinical studies. These claims need to be validated with real-world evidence, and the es-

tablishment of EU RWE and registries is critical.[21] Challenges in developing RWE data encompass informed consent, stakeholder involvement, patient outcomes, data collection, motivation and reward, as well as data privacy and retention.[13]

By addressing these issues, healthcare systems can better assess the value and affordability of specialised therapeutics and ensure that the benefits of these innovative treatments are accessible to patients in need. Moreover, refining HTA processes and negotiation strategies, as well as incorporating RWE and adaptive payment models, will be critical to facilitate the adoption of specialised therapeutics in the rapidly evolving healthcare landscape.

Integrating real-world evidence and innovative pricing approaches

Although the new EU JCA regulation represents a significant advancement in addressing market access challenges for innovative pharmaceuticals, further enhancements are required to fully realise the potential of these therapies. Adaptive models incorporating real-world evidence and innovative pricing strategies are critical to ensure that novel pharmaceuticals are accessible and affordable for patient.[21]

Real-world-evidence in HTAs: The use of real-world evidence in HTAs can help reduce uncertainty about the long term efficacy and safety of innovative pharmaceuticals and provides additional data to support reimbursement decisions. Sources of real-world data (RWD) include electronic health records, patient registries, and national databases.[25] These sources can be used to generate RWE, which can complement traditional randomised controlled trials (RCTs) and provide a more comprehensive understanding of a pharmaceutical's performance in real-world scenarios.[4]

Value-based pricing (VBP) for innovative pharmaceuticals: Innovative pricing strategies, such as value-based pricing (VBP) can facilitate alignment between the cost of novel pharmaceuticals and their clinical and economic benefits, thereby improving affordability and access for patients. In VBP, prices are set based on the therapeutic value a pharmaceutical offers in terms of improved health outcomes or reduced healthcare expenditure. This approach has become increasingly popular in recent years as a means to better balance innovation incentives and budget constraints in the healthcare system.[15]

Risk-sharing agreements (RSAs) in reimbursement: Risk-sharing agreements between manufacturers and payers can help manage the uncertainties associated with innovative pharmaceuticals by linking reimbursement to predefined clinical or economic outcomes. RSAs, also referred to as performance-based risk-sharing arrangements (PBRSAs), can take several forms, including outcomes-based agreements and finance-based agreements.[5] These agreements are intended to reduce financial risk for payers while promoting access to new therapies.

Real-world evidence and adaptive payment models: Highly effective therapies have the potential to enhance efficiency by decreasing long-term hospital treatments. However, these efficiency gains are seldom demonstrated in short-term clinical studies. These claims need to be validated with RWE, which makes the establishment of EU RWE and registries essential. Challenges in developing RWE data include informed consent, stakeholder involvement, patient-centred outcomes, data acquisition, and data protection.[21]

The US and EU have different approaches to RWE, with the US Food and Drug Administration (FDA) actively seeking opportunities to include RWE in regulatory decision-making, while the EMA takes a more cautious stance on

RWE due to concerns about data quality and representativeness.[10]

Conclusion:

The EU Joint Clinical Assessments (JCA) regulation offers a promising solution to address market access challenges associated with innovative pharmaceuticals. Nevertheless, to fully exploit the potential of innovative pharmaceuticals, it is essential to integrate RWE and adopt innovative pricing strategies, such as VBP and RSAs. The assessment of specialised therapeutics requires a shift in the current HTA process to better accommodate innovative treatments. By addressing these challenges, the regulation can enable the introduction of novel therapies, ultimately benefiting patients and healthcare systems across the European Union.

The success of the EU regulation on the Joint Evaluation of Medicinal Products depends on active collaboration and commitment. Moreover, the inclusion of real-world evidence in the HTA process can also help to address uncertainty about the long-term efficacy and safety of innovative pharmaceuticals.[25]

These data can provide additional evidence to support reimbursement decisions and can be obtained from sources such as electronic health records, patient registries, and claims databases.[4] Furthermore, innovative pricing strategies, such as value-based pricing (VBP), can help ensure that the cost of novel pharmaceuticals aligns with their clinical and economic benefits, improving affordability and access for patients.

Another important aspect of market access for innovative pharmaceuticals is the adoption of risk-sharing agreements (RSAs) between manufacturers and payers. These agreements link reimbursement to predefined clinical or economic outcomes, reducing financial risk for payers while promoting access to new therapies.[15] RSAs can take various forms, including outcomes-based agreements and finance-based agreements.[5]

Finally, the establishment of EU RWE and registries is critical for validating claims of improved efficiency and reductions in hospital treatments related to specialised therapeutics.[21] Challenges in developing RWE data include informed consent, stakeholder involvement, patient-centred outcomes, data collection, and data protection.[21]

The US and EU have different approaches to RWE, with the US Food and Drug Administration (FDA actively seeking opportunities to include RWE in regulatory decision-making, while the EMA takes a more cautious stance on RWE due to concerns about data quality and representativeness.[10]

In summary, the EU JCA regulation represents a significant step forward in addressing market access challenges for innovative pharmaceuticals, particularly specialised therapeutics. The streamlining of the HTA process, increased transparency, and enhanced collaboration among EU member states have the potential to facilitate market access for transformative therapies [29]

The integration of RWE and innovative pricing strategies, such as VBP and RSAs, can help ensure that novel pharmaceuticals are accessible and affordable for patients, while also addressing uncertainties regarding clinical outcomes and cost-effectiveness.[16] By actively collaborating and refining the regulatory framework, the EU can establish a more adaptable and collaborative HTA environment that accelerates the adoption of groundbreaking therapies, ultimately enhancing patient access and healthcare outcomes across Europe.

References

[1] Agnelli G, Beyer-Westendorf J, De Caterina R & Raskob GE (2019). Precision medicine in anticoagulation therapy: focus on individual benefit and risk. Journal of Thrombosis and Haemostasis, 17(6), 911-924.

[2] Alliance for Regenerative Medicine (Allianz für Regenerative Medizin) (2020).

Global Regenerative Medicine Sector Report: H1 2020. Retrieved from https://go.sn.pub/1Tdb1i

[3] Angelis A, Lange A & Kanavos P (2018). Using health technology assessment to assess the value of new pharmaceuticals: Results of a systematic review and expert consultation across eight European countries. The European Journal of Health Economics, 19(1), 123-152.

[4] Berger ML, Sox H, Willke RJ, Brixner DL, Eichler HG, Goettsch W, ... & Tarricone, R (2017). Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE special task force report. Value in Health, 20(8), 1003-1008.

[5] Carlson JJ, Sullivan SD, Garrison LP, Neumann, PJ & Veenstra DL (2010). Linking payment to health outcomes: A taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers. Health policy, 96(3), 179-190.

[6] Chambers JD, Panzer AD & Neumann PJ (2019). Variation in US private health plans' coverage of orphan drugs. The American Journal of Managed Care, 25(10), 508-512.

[7] Darrow JJ, Avorn J & Kesselheim AS (2020). The FDA breakthrough-drug designation – Four years of experience. The New England Journal of Medicine, 378(15), 1444-1453.

[8] Dranitsaris G, Truter I, Lubbe MS, Amir E & Evans WK (2015). Biosimilars of biological drug therapies: regulatory, clinical and commercial considerations. Drugs, 75(13), 1467-1473.

[9] Eichler HG, Baird LG, Barker R, Bloechl-Daum B, Børlum-Kristensen F, Brown J, ... & Haigh, J (2015). From adaptive licensing to adaptive pathways: Delivering a flexible life-span approach to bring new drugs to patients. Clinical Pharmacology & Therapeutics, 97(3), 234-246.

[10] Eichler HG, Koenig F, Arlett P, Enzmann H, Humphreys A & Pétavy F (2021). Generating real-world evidence in the European Union: The Innovative Medicines Initiative's DIRECT project. Clinical Pharmacology & Therapeutics, 109(3), 616-623.

[11] European Commission (2021). Proposal for a Regulation of the European Parliament and of the Council on health technology assessment and amending Directive 2011/24/EU. Retrieved from https://go.sn.pub/zRHWS3

[12] Ferrario A, Arāja D, Bochenek T, Catic T, Dankó D, Dimitrova M, ... & Jakupi, A (2017). The implementation of managed entry agreements in Central and Eastern Europe: findings and implications. PharmacoEconomics, 35(12), 1271-1285.

[13] Franklin JM, Glynn RJ, Martin D & Schneeweiss S (2020). Evaluating the use of nonrandomized real-world data analyses for regulatory decision making. Clinical Pharmacology & Therapeutics, 107(4), 843-852.

[14] Gammie T, Lu CY & Babar ZUD (2016). Access to orphan drugs: a comprehensive review of legislations, regulations and policies in 35 countries. PLoS One, 11(10), e0164090.

[15] Garrison LP Jr, Neumann PJ, Erickson P, Marshall D & Mullins CD (2007). Using real-world data for coverage and payment decisions: the ISPOR real-world data task force report. Value in Health, 10(5), 326-335.

[16] Garrison LP, Jackson T, Paul D & Kenston M (2019). Value-based pricing for emerging gene therapies: The economic case for a higher cost-effectiveness threshold. Journal of Managed Care & Specialty Pharmacy, 25(7), 793-799.

[17] Husereau D, Henshall C & Sampietro-Colom L (2020). Changing health technology assessment paradigms? International Journal of Technology Assessment in Health Care, 36(1), 1-4.

[18] Jørgensen J & Kefalas P (2015). Reimbursement of licensed cell and gene therapies across the major European healthcare markets. Journal of Market Access & Health Policy, 3, 29321.

[19] Jørgensen J , Hanna E & Kefalas P (2018). Outcomes-based reimbursement for gene therapies in practice: The experience of recently launched CAR-T cell therapies in major European countries. Journal of Market Access & Health Policy, 6(1), 1549927.

[20] Kristensen FB, Husereau D, Huić M, Drummond M, Berger ML, Bond K, ... & Ollendorf, D. A (2019). Identifying the need for good practices in health technology assessment: Summary of the ISPOR HTA Council Working Group Report on good practices in HTA. Value in Health, 22(1), 13-20.

[21] Makady A, de Boer A, Hillege H, Klungel O & Goettsch W (2017). What is real-world data? A review of definitions based on literature and stakeholder interviews. Value in Health, 20(7), 858-865.

[22] Mestre-Ferrandiz J, Palaska C, Kelly T & Hutchings A (2019). The current HTA landscape for cell and gene therapies in Europe. Journal of Market Access & Health Policy, 7(1), 1648974.

[23] Milea D, Nestler-Parr S, Chesney C, Chicoye L, Espín J, Kanters S, ... & Toumi, M (2017). A review of NICE appraisals of pharmaceuticals 2000-2016 found variation in establishing comparative clinical effectiveness. Journal of Clinical Epidemiology, 84, 1-9.

[24] Picavet E, Cassiman D, Aertgeerts B & Willems L (2013). ChondroCelect® in the treatment of cartilage defects of the knee: a systematic review of clinical trials. Knee Surgery, Sports Traumatology, Arthroscopy, 21(11), 2634-2642.

[25] Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, ... & Woodcock, J (2016). Real-world evidence – What is it and what can it tell us? The New England Journal of Medicine, 375(23), 2293-2297.

[26] Sorenson C, Drummond M & Kanavos P (2015). Ensuring value for money in health care: The role of health technology assessment in the European Union. Observatory Studies Series, 11.

[27] Tafuri G, Pagnini M, Moseley J, Massari M, Petavy F, Behring A, ... & Pani, L (2016). How aligned are the perspectives of EU regulators and HTA bodies? A comparative analysis of regulatory-HTA parallel scientific advice. British Journal of Clinical Pharmacology, 82(4), 965-973.

[28] Toumi M, Rémuzat C, Vataire AL & Urbinati D (2014). External reference pricing of medicinal products: Simulation-based considerations for cross-country coordination. European Journal of Health Economics, 15(7), 779-789.

[29] Vella Bonanno P, Bucsics A, Simoens S, Martin AP, Oortwijn W, Gulbinovič J, Rothe CC, Timoney A, Ferrario A, Gad M, Salem AH, Hoxha I, Sauermann R, Kamusheva M, Dimitrova M, Laius O, Selke G, Kourafalos V, Yfantopoulos J, ... Godman, B (2019). Proposal for a regulation on health technology assessment in Europe – opinions of policy makers, payers and academics from the field of HTA. Expert Review of Pharmacoeconomics & Outcomes Research, 19(3), 251-261. https://go.sn.pub/3BToKN

Methods for indirect treatment comparisons - a case analysis

Professor Heiner C. Bucher MD, MPH | Emeritus Professor for Clinical Epidemiology, Department of Clinical Epidemiology, University Hospital Basel

In Germany, the medical additional benefit of pharmaceuticals for the treatment of rare diseases – so-called orphan drugs – receiving marketing authorisation in the European Union is considered to be proven within the scope of marketing authorisation. According to the requirements of the Federal Joint Committee (G-BA), only the extent of the additional benefit must be proven based on the marketing authorisation data. Due to low case numbers, applicants predominantly determine the extent of the additional benefit of orphan drugs based on indirect comparisons of the pivotal study and external control groups. Due to this approach, the G-BA assessed the additional benefit as unquantifiable in 19 out of 20 (95%) orphan drug application processes from early 2017 through April 2022. The deficiencies of an AMNOG application based on an indirect comparison of the pivotal study with historical external control groups and the possibilities for a more stringent approach by emulating a target trial are outlined based on the case study of avapritinib.

Introduction

Rare diseases (orphan diseases) are defined as diseases that do not affect more than one person per 2,000 inhabitants and often cause serious, chronic health problems involving several organ systems.[1] For pharmaceuticals for the treatment of rare diseases, so-called orphan drugs, which are approved in the European Union, the additional medical benefit is considered to be proven by the approval according to SGB V in Germany, without having to provide evidence of the additional medical benefit with a comparative therapy according to the specifications of the Joint Federal Committee (G-BA) (Section 35a Paragraph 1 Sentence 11 2nd half sentence SGB V). Only the extent of the additional benefit based on the approval data must be substantiated (Section 5 (8) AM-NutzenV).

Due to the small number of patients suffering from orphan diseases, registration studies are generally not based on randomised controlled studies. In a not yet published analysis of the German Pharmaceutical Market Reorganisation Act (AMNOG), approval procedures based on non-randomised controlled trials (RCT), between 1 January 2017 to 1 April 2022 no evidence from RCTs was available for 42 procedures for a total of 37 pharmaceuticals out of 215 initial evaluations.[2]

The European Medicines Agency (EMA) took into account all single-arm trials (SAT), while the G-BA only considered 20 (47.6%) procedures, all of which related to orphan drugs. However, in 19 out of 20 studies on orphan drug, the G-BA assessed the additional benefit as not quantifiable. The discrepancy in the evaluation of evidence from non-randomised studies in the benefit-risk assessment upon approval by the EMA and in the evaluation of the additional benefit by means of the AMNOG procedures by the G-BA raises fundamental questions.

Only in an extremely low percentage, the G-BA is willing

to consider the additional benefit of new pharmaceuticals or new treatment indications that are not documented by means of randomised controlled studies. This particularly applies to orphan diseases, where approval by the EMA already implies proof of a positive benefit-risk assessment. Here, the G-BA assesses the additional benefit as „not quantifiable" in 95% of all submissions on orphan drugs.

This restrictive position is also supported by the IQWIG, which states that only „in case of extremely rare diseases or extremely specific disease constellations (...) the requirement for (parallel) comparative studies [may be] inappropriate".[3]

The question thus arises as to how, in case of rare or extremely rare diseases, evidence from non-randomised controlled studies can be better and more bindingly included in AMNOG procedures for the assessment of the additional benefit. For this purpose, general methodological guidelines have been developed by the IQWIG.[4,5] On the basis of a case study, the evidence and decision-making basis of a current AMNOG procedure on an indirect comparison procedure for the documentation of an additional benefit an orphan drug provides will be examined.

Professor Heiner C. Bucher MPH, *Specialist in General Internal Medicine and Prevention and Public Health (FMH), Emeritus, Professor of Clinical Epidemiology, University of Basel and Consultant, Department of Infectious Diseases and Hospital Hygiene, University Hospital Basel 2001-2021. Research stays in the USA and Canada. The method for indirect comparisons developed by Professor Bucher has been widely used in the HTA field and was the starting point for the development of the network meta-analysis technique.*

The case study

Avapritinib (Ayvakyt®) is a small molecule inhibitor that received orphan drug designation in 2018 and was approved for the treatment of patients with inoperable or metastatic gastrointestinal stromal tumours (GIST) with PDGFRA-D842V mutation. On 24 March 2022, the orphan drug designation of avapritinib was confirmed by the EMA in the new indication of adults with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematologic neoplasia (SM-AHN), or mast cell leukaemia (MCL) after they have received at least one systemic therapy. The pharmaceutical company (pU) submitted a dossier to the G-BA in due time to determine the additional benefit of avapritinib in this new indication.

The dossier and its assessment will be discussed in detail below for the endpoint survival time, as an indirect comparison is only available for this endpoint. However, the analysis of other important endpoints, such as adverse events, is beyond the scope of this article.

The disease pattern

Systemic mastocytosis (SM) is a neoplastic disease of atypical spindle-shaped blood mast cells with infiltration of bone marrow, skin and organs, such as the liver, spleen, lymph nodes, and intestine.[6] A distinction is made between an indolent SM (ISM), which has little organ invasion and little or no effect on patient survival, and an organ invasive form (AdvSM), which leads to death after 0.2 to 5.7

years, depending on the mode of progression.[6,7]

In 80 to 95% of all SM patients, the cause of the disease is a mutation of the tyrosine kinase receptor (KIT) (mutation-D816, of which >95% are KIT D816V), as well as other rare additional mutations. The D816 mutation leads to ligand-independent KIT activation and clonal expansion of atypical mast cells with organ infiltration.

Avapritinib is a highly selective and potent type I tyrosine kinase inhibitor with activity against KIT exon 17 mutations, and in particular the most common mutation D816V, which selectively inhibits clonal expansion of mast cells. Therapeutic options for the treatment of AdvSM are limited and focused on symptom control therapies. Targeted therapy using the only approved multikinase inhibitor, midostaurin, is of limited efficacy, with an overall response rate of 30%, a remission rate of < 1%, and a median overall survival of 26.8 months for all AdvSM patients.[8, 9]

Evidence in the avapritinib module 4A regulatory dossier Methods and statistical procedures

The pharmaceutical company documents the extent of additional benefit for overall survival based on the pivotal phase II PATHFINDER study (BLU-285-2102) and the dose-escalation study EXPLORER of patients following systemic therapy who received the initial dose of 200mg avapritinib per day using a propensity score (PS)-adjusted indirect comparison with historical data of patients with the same underlying condition from hospital records in the EU and the US (BLU-285-2405).[10]

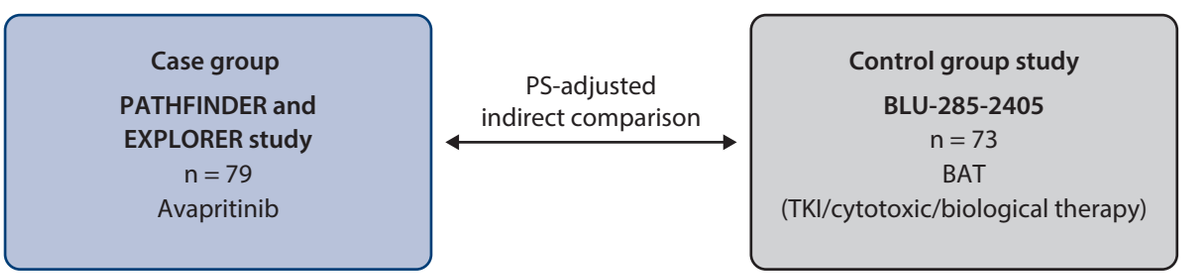
The PATHFINDER and EXPLORER studies collected data on patient-relevant outcomes of mortality, morbidity, health-related quality of life, safety of the pharmaceutical, and surrogate parameters (particularly mutation scores). However, in the historical control study, only endpoint data on survival, duration of response and a single surrogate parameter, tyrosine kinase activity, were available.

Study populations included patients who were considered assessable at baseline according to the Modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and the European Competence Network on Mastocytosis (mIWG), had received at least six 28-day cycles of avapritinib at an initial dose of 200mg/day, had at least two bone marrow aspirates performed at the end of treatment, and were available at the end of the study. The index date was the date of receipt of initial systemic therapy. 79 patients treated with avapritinib with 79 lines of treatment (LOTs) from the PATHFINDER and EXPLORER studies were analysed, as well as 73 patients from the BLU-285-2405 study with 104 LOTs treated with best alternative therapy (BAT) with alternative tyrosine kinase inhibitors (TKIs) or by cytotoxic or biologic therapies (see figure 1). Patients of the BLU-285-2405 control cohort had to be assessable at baseline according to mIWG criteria, have a performance score, and have an index visit of at least three months prior to first system therapy and a follow-up of at least 168 days.

The index date was the receipt of first systemic therapy between 2009 and 2021. Some patients in the BAT cohorts thus underwent multiple therapy cycles and could subsequently also be treated with avapritinib. According to the pharmaceutical company, data were collected from a total of 161 patients in the BAT cohort treated in the study centres between 2009 and 2021, of whom 20 were excluded due to missing covariates. The initial analysis population thus consisted of 141 patients in the BAT cohort and 176 patients in the avapritinib cohorts.

For the indirect comparison of overall survival, the pharmaceutical company used an inverse probability of treatment weighting (IPTW) method to adjust for differences in the distribution frequency of relevant cofactors between

Number of patients treated with avapritinib and with best alternative therapy (BAT) with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasia (SM-AHN) or mast cell leukaemia (MCL) in the indirect comparison study



TKI, tyrosine kinase inhibitor ; BAT, best alternative therapy

Source: Blueprint Medicines (Germany) GmbH as local representative of the marketing authorisation holder Blueprint Medicines (Netherlands) B. V. Dossier for the benefit assessment according to Section 35a SGB V Avapritinib (AYVAKYT®) Module 4 A. 1 April 2022.

Figure 1: The PATHFINDER and EXPLORER studies collected data on patient-relevant outcomes of mortality, morbidity, health-related quality of life, safety of the pharmaceutical, and surrogate parameters.

treatment groups and calculated standardised differences for the avapritinib and BAT cohorts. A standardised difference of >10% was considered a relevant imbalance between the two comparison groups. Table 1 shows that for several prognostic factors (including tyrosine kinase) that were included in the PS, relevant imbalances between treatment groups remained after weighting.[10]

The PS and weights were estimated using a logistic regression model, and the weights were stabilised for each LOT by the marginal likelihood of being in the respective treatment group. In addition, the stabilised weights were capped at the 1st and 99th percentiles. Overall survival estimates were calculated using a weighted Cox regression model with robust sandwich variance estimators that included the treatment variable and any key covariates that remained unbalanced after weighting with stabilised IPTW weights. A graphical representation of the overlap of the unweighted and weighted dataset was omitted by the pharmaceutical company. Sensitivity analysis for the endpoint overall survival was also missing.

Study results on overall survival

After a median follow-up time of 11.2 and 72.7 months in the comparison groups of patients treated with avapritinib and BAT, respectively, the hazard ratio (HR) for overall survival was 0.37 (95% CI 0.18-0.75) for patients treated with avapritinib versus those treated with BAT (table 2).[10] The median survival time was not reached at the time of the interim analysis of patients treated with avapritinib.

After a median follow-up of 13.4 and 14.3 months, re-

Indirect comparison of patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasia (SM-AHN) or mast cell leukaemia (MCL) treated with avapritinib and the best alternative therapy (BAT).

	Unweighted sample			IPTW-weighted sample		
	Avapritinib (200 mg/Tag)	BAT	Standardised difference	Avapritinib (200 mg/Tag)	BAT	Standardised difference
Data cut-off 20 April 2021/04. October 2021						
Safety-Population						
Number of patients N	79	73	–	77	66	–
Number of therapy lines (LOT)	79	104		77	96	
AdvSM subtype diagnosis, n (%)						
SM-AHN	48 (60.8 %)	53 (51.0 %)	19.8 %	42.3 %	45.5 %	6.4 %
ASM	15 (19.0 %)	26 (25.0 %)	14.6 %	28.5 %	24.6 %	8.8 %
MCL	16 (20.3 %)	25 (24.0 %)	9.1 %	29.2 %	29.9 %	1.5 %
Skin involvement, n (%)						
Any involvement of the skin	28 (35.4 %)	37 (35.6 %)	0.3 %	39.6 %	34.9 %	9.8 %
Leukocyte count, n (%)						
≥16 × 10^9/l	12 (15.2 %)	25 (24.0 %)	22.4 %	13.1 %	19.8 %	18.2 %
Serum tryptase, n (%)						
≥125 ng/ml	62 (78.5 %)	68 (65.4 %)	29.5 %	77.9 %	73.0 %	11.3 %
SRSF2/ASXL1/RUNX1 (S/A/R) mutation panel, n (%)						
Number of patients tested for at least one mutation	79 (100 %)	79 (76.0)	–	100 %	65.4 %	–
KIT mutation, n (%)						
Tested patients	75 (94.9 %)	103 (99.9 %)	–	95.9 %	99.0 %	–
Wild type	4 (5.3 %)	10 (9.7 %)	–	2.8 %	8.6 %	–
KIT mutation	71 (94.7 %)	93 (90.3 %)	–	97.2 %	91.4 %	–
ECOG						
n (%)	79 (100 %)	104 (100 %)	–	100 %	100 %	–
Mean (SD)	1.2 (0.9)	1.0 (0.7)	–	1.1 (0.8)	1.1 (0.7)	–
Anaemia						
n (%)	46 (58.2 %)	71 (68.3 %)	20.9 %	62.0 %	63.1 %	2.3 %
Thrombocytopenia						
n (%)	31 (39.2 %)	66 (63.5 %)	49.9 %	42.2 %	49.7 %	15.1 %

Source: Blueprint Medicines (Germany) GmbH as local representative of the marketing authorisation holder Blueprint Medicines (Netherlands) B. V. Dossier for the benefit assessment according to Section 35a SGB V Avapritinib (AYVAKYT®) Module 4 A. 1 April 2022.

Table 1: In the BAT cohort, data were collected from a total of 161 patients treated in the study centres between 2009 and 2021, of whom 20 were excluded due to missing covariates.

Probability of survival of patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasia (SM-AHN) or mast cell leukaemia (MCL) with avapritinib or best alternative therapy (BAT).

	Avapritinib (200 mg/day)	BAT
Unweighted population		
Data cut-off	20. April 2021	04. Oktober 2021
Number of patients N	79	73
Number of therapy lines (LOT)	79	104
PS-adjusted indirect comparison (IPTW adjusted population)		
Number of patients N	77	66
Number of therapy lines (LOT)	77	96
Event, n (%)	13 (16.9)	44 (66.7)
Censored patients, due to initiation of treatment with avapritinib, n (%)	–	8 (12.1)
Censored patients due to a new primary malignancy after the index date, n (%)	–	3 (4.5)
Follow-up time (months) median [95% CI]	11.2 [7.5; 15.4]	72.7 [32.8; 109.5]
Hazard ratio (HR)	0.37 (95 %-KI 0.18–0.75)	

Source: Blueprint Medicines (Germany) GmbH as local representative of the marketing authorisation holder Blueprint Medicines (Netherlands) B. V. Dossier for the benefit assessment according to Section 35a SGB V Avapritinib(AYVAKYT®) Module 4 A. 1 April 2022

Table 2: After the follow-up time, the hazard ratio (HR) for overall survival for patients treated with avapritinib versus those treated with BAT was 0.37 (95% CI 0.18-0.75)

spectively, 80.5% of patients with SM-AHN and 75.0% of patients with MCL were still alive.

Assessment of the evidence by the G-BA

In its decision of 15 September 2022, the G-BA states that „based on the submitted indirect comparisons (...) no statement on the extent of additional benefit [can be made]... as only single-arm data are available, and a comparative assessment is not possible. In the overall view, an indication of a non-quantifiable additional benefit was identified for avapritinib, since the scientific data basis does not allow quantification."[11]

In its justification, the G-BA particularly criticises a clear definition of BAT. Furthermore, inclusion and exclusion criteria between the comparison cohorts were inconsistent, especially for the confirmation type of AdvSM diagnosis, measurable C-criteria (blood count abnormality, such as anaemia and thrombocytopenia), pathological liver values, clinical criteria (e.g. splenomegaly), other laboratory parameters, quality of life parameters as well as comorbidities.

Moreover, there was a „lack of a systematic literature search and assessment to identify confounders for the question addressed in the benefit assessment." Regarding the analysis, the G-BA criticises that in the analysis of overall survival (OS), standardised differences of >10% between the comparison groups, defined as relevant, remained for 7 of 13 key covariates after propensity score adjustment.

The lack of the following covariates in the analysis is mentioned as worth considering: BMI (body mass index), number of co-mutations, mast cell infiltration in bone marrow or presence of mast cell aggregates, various laboratory measurements, comorbidities, symptoms associated with mast cell activation, stem cell transplantation, and place of treatment.

Critical assessment of the application procedure of the pharmaceutical company and the assessment by the G-BA

Data collection from individual studies, registries or electronic patient records for comparative studies without randomisation is generally accepted by IQWIG and thus also by the G-BA for benefit assessment, provided that „data relevant to the specific research question are available in such a quality that the analyses can be interpreted with sufficient certainty in the context of a registry study."[5] Regarding the statistical models to be used, the IQWIG limits itself to very general guidelines with little detail and is open with regard to the various models for confounder-adjusting (e.g. propensity score).

It is obvious that a detailed study protocol with systematic identification and inclusion of all relevant confounders, as well as a comprehensible statistical analysis plan for all patient-relevant outcomes are prerequisites for an AMNOG submission. The importance of the methodological procedure for the elimination as well as the transparent presentation of the minimisation of biases, which are significant for protocol development and analysis of special observational study data, was presented in a previous article.[12] In particular, the problem areas of the avapritinib input and ways to improve it will be explained here.

The flow diagrams of the safety population of patients treated with avapritinab do not conclusively show which criteria led to the inclusion of patients in the final analysis and the same applies to the control cohort. Since approximately 50% of the safety population was not included in the indirect comparison, questions arise about the external validity of the results. In addition, the PATHFINDER study included two cohorts of patients (n=63) with C criteria and without C criteria (n=40). No stratified analysis was performed for the overall survival endpoint, which would have been desirable due to prognostic differences. To minimise the risk of selection bias, a total of eight patients in the control cohort who later received avapritinib were included in this group and censored upon receipt of study drug. Since patients in the control cohort could receive multiple systemic treatments, a robust variance estimation method was used.

Regarding prior systemic therapies with the tyrosine kinase inhibitor midostaurin and cladribine, a cytotoxic agent, there were significant differences in the comparator cohorts: Midostaurin was the relevantly more frequently used first systemic therapy in avapritinib-treated patients. However, according to an analysis of German registry data, this seems to be more effective than cladribine treatment.[13] Moreover, the side effect profile with treatment discontinuations is more severe with midostaurin[14] than with cladribine[15]. This constellation favours a selection bias in which those treated with midostaurin are theoretically more likely to receive therapy with avapritinib.

The lack of a systematic literature search to identify confounders was criticised by the G-BA. For ASM, there was a „global prognostic score for overall survival" (GPSM-OS) that was developed on an extensive diagnostic and validation cohort of 422 and 853 patients in each case and includes the singular independent prognostic variables haemoglobin ≤110 g/l, serum alkaline phosphatase ≥140 IU/l, and at least one of the following mutations SRSF2, ASXL1,

RUNX1, or DNMT3A.[16] The C-index, a measure of the quality of a prognostic score, was 0.72 [0.66-0.78] for GPSM-OS overall survival for patients with ASM.

Unfortunately, in the present study mutation data and serum alkaline phosphatase, a proxy parameter for bone infiltration, were missing for 25% of the control cohort. In the prognostic GPSM study, serum tryptase concentration, which correlates with mast cell burden, was a prognostic marker for progression-free but not overall survival.[16] The important GPSM study was not included in the analysis by the pharmaceutical company.

After the weighting procedure, there was still a more than 10% difference between the comparison groups for some weighty covariates (e.g. leukocyte count, thrombocytopenia, tyrosine kinase). This prompted the pharmaceutical company to take the unusual step of including these variables in the logistic regression model in addition to the PS weighting variable. It is unclear whether these variables may thus have been included twice in the model. However, such poor model specifications increase the risk of bias.[17,18] Because of the choice of a historical control group, values for both important covariates and end points were missing. Detailed information on imputation procedures of missing covariates could not be identified.

Despite the data-related methodological limitations of the present indirect comparison and a limited observation period, there is evidence that avapritinib relevantly improves several disease parameters, such as reduction in bone marrow infiltration and improvement in haematopoiesis, reduction in important surrogate parameters such as serum tryptase and the KIT D816V mutation, as well as a 20% complete remission rate. These changes provide reasonable hope for a prolonged response rate, improved prognosis, and quality of life for patients treated with avapritinib.

Alternative approaches of observational data analyses for indirect comparisons

The application discussed here illustrates the methodological problems and biases of an indirect comparison based on historical comparative data from patient records from multiple treatment centres. The basic principles of alternative approaches of a more stringent data analysis will be outlined below. In principle, any clinical question such as the one presented here of a survival benefit of avapritinib in patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematologic neoplasia (SM-AHN), or mast cell leukaemia (MCL) compared with BAT can be addressed in a randomised target trial (table 3). If randomisation is not possible, a target trial can be performed using observational data.[19]

By this we understand the development of a comparative design based on observational data that, except for the lack of randomisation, has the closest possible approximation to a pragmatic RCT in the study design. Target trials can only be perceived as pragmatic trials, which have no placebo group, no blinded patient assignment, and no blinded endpoint determination-things that also do not occur in clinical practice.[20]

Randomisation of comparison groups ensures comparability of treatment groups against all known and unknown confounders and allows the establishment of a causal relationship between an exposure (intervention) or no exposure (control group) and an outcome. Measuring as many relevant confounders as possible before the start of an exposure (i.e. intervention or control treatment) allows the broadest possible control of a selection bias in a target trial. Another advantage of randomisation is the clear start of exposure (time 0 at randomisation). This point is important for the determination of a causal relationship in observational data analysis.

Profile of a Target Trial Protocol: Specification and emulation based on data from an observational study

Protocol components	Description	Example: ASM, SM-AHN or MCL	
		Specification	Emulation by cohort study
Inclusion criteria	Who will be included in the study?	Individuals ≥18 years with ASM, SM-AHN or MCL with ≥1 systemic therapy*.	Same as for specification
Treatment strategies	What interventions will individuals to be included receive?	Treatment with avapritinib Treatment with BAT#	Same as for specification Relevant confounders are defined and collected at time 0 and time-dependent confounders± are defined and collected at follow-up
Treatment allocation	How are individuals to be included assigned to an intervention?	Individuals to be included are openly randomised to one of the interventions to be tested	Individuals to be included are assigned to the intervention for which the data are compatible at time 0.
Endpoints	Which endpoints are compared between the treatment groups for individuals to be included?	Death	Same as for specification
Follow-up	Over which period of time are individuals included in the study followed up?	From randomisation to death, loss to follow-up, administrative censoring, whichever comes first.	Same as for specification Required data: Date of end of follow-up or censoring
Causal estimand	Which counterfactual contrasts are measured?	Intention to treat effect (effect of randomised intervention allocation) Per protocol effect (effect of intervention as assigned in protocol)	Observationally equal to the per protocol effect
Statistische Analyse	How are the counterfactual contrasts estimated?	Intention to treat analysis Per protocol analysis (conditional adjustment for confounders at randomisation and confounders after randomisation)	Same as per protocol analysis (conditional adjustment for confounders at randomisation and confounders after randomisation)

*The systemic therapy in question and/or its components must be defined; # BAT is precisely defined (with inclusion and exclusion criteria) according to consultation with experts and the G-BA; ± Confounders are identified after a systematic literature search and expert consultation and specified and hierarchised in a causal diagram using directed acyclic graphs (DAG);
ASM, aggressive systemic mastocytosis; SM-AHN, systemic mastocytosis with associated haematological neoplasia; MCL mast cell leukaemia

Source: Hernan MA. Methods of Public Health Research - Strengthening Causal Inference from Observational Data. N Engl J Med. 2021;385(15):1345-1348.

Table 3: In principle, any clinical question can be addressed in a randomised target trial. If randomisation is not possible, a target trial can be performed using observational data.

The first step in target trial emulation is the development of a target trial protocol specifying inclusion criteria, treatment strategies to be evaluated, timing of subject inclusion and censoring of follow-up, endpoints, and causal

contrasts or estimates in an analysis plan to answer the causal question (effect of treatment A versus B in population Z on outcome Y).

The second step is to emulate the study using observational data by identifying eligible subjects, treatment allocation (as done and documented in practice), defining follow-up from treatment initiation to censoring, and adjusting for relevant confounders at inclusion, and if necessary, time-dependent confounders during follow-up. Significant importance is attached to the time of inclusion to avoid immortal bias.[20] For each subject eligible for the respective therapy (treatment A or B), „time" is considered to be the time when all inclusion criteria are fulfilled, and treatment (with A or B) is performed. This strategy avoids comparing subject who have received relevant prior therapies or the therapy under evaluation before time 0 (so-called „prevalent users") with „never users".

Subjects can be included for a longer period or several times for one of the two therapies (A or B) of a target trial. In this case, for example, only the first therapy or the therapy existing at a random time point can be selected. If there is fixed data collection in a cohort (e.g. every six months), a new study can be emulated at each fixed time point of data collection using an established study design.

For variable multiple measurement points, e.g. a short fixed period (e.g. one month) can be chosen and a study emulated at each new time point.[21] This means that a target trial constructed can be constructed from X sub-trials corresponding to the number of relevant measurement points.

The latter approach increases the efficiency of a target trial but requires necessary adjustments of the variance estimators. It is also possible to include tolerance periods (grace period), e.g. plus three months from time 0, in a target trial. For this period, a subject can be included for both treatment strategies (A or B). If the endpoint of interest occurs during the grace period, the subject can be randomly assigned to a treatment strategy. Alternatively, it is possible to create two copies (clones) for the respective patient and randomly assign each clone to a treatment strategy.

Clones are then stopped and censored at the time consistent with the assigned treatment strategy. Potential biases due to this informative censoring must be controlled using time-dependent confounder adjustment and inverse weighting procedures.[22] Clearly, the approach of including grace periods and cloning is not consistent with an intention-to-treat analysis and therefore estimates a per protocol effect of a target trial.

The adjustment of different distributions of confounders at inclusion or during follow-up is performed with inverse weighting methods such as PS, marginal structured models or g-estimation.[22,23] Target trial emulation can only lead to a more transparent and improved estimation of a treatment benefit using observational data if all relevant confounders have been measured and the problem of missing data is limited. Thus, target trial emulation is ideally based on prospectively collected data from a cohort study or a patient registry of high data quality.

Discussion and conclusions

This critical assessment of an AMNOG application based on data from non-randomised controlled studies is limited to the methodological and analytical aspects of an indirect comparison of a single-arm study with a historical control arm regarding one endpoint, overall survival. An overall assessment of the evidence, in particular regarding the data on adverse effects presented by the applicant – which were not assessed here – was not the aim of the present analysis. Thus, no comment is made on the decision of the G-BA on the application to quantify the added benefit of ava-

pritinib. The methodological problems and biases resulting from the choice of a historical comparison group from hospital records highlight the need for alternative approaches to study design, for example using target trial emulation.

The French Haute Autorité de Santé (HAS) has recently specified its requirements regarding the use of target trial emulation for HTA reports that are not based on randomised controlled data.[24] A crucial first step of the procedure according to HAS is the justification of the non-feasibility of randomisation by the applicant. The basic conditions of an analysis by means of external controls using a target trial emulation are explained below. Various HTA organisations in the EU emphasise the exceptional situation for applications that are not based on randomised evidence.

However, especially for orphan drugs and diseases, the question arises to include more binding criteria that give applications based on non-randomised evidence a fair chance for reimbursement. Such a catalogue of criteria would have to be associated with the creation of further detailed criteria for protocol development, e.g. by means of target trial emulation and data analysis of observational studies. Mandatory with this step would be adapted assessment criteria for observational studies regarding data analysis as well as internal and external validity of the results.

Existing validity criteria that assess the bias susceptibility of results according to RCT criteria, such as blinded randomisation, blinded intervention, and endpoint determination, as well as an intention-to-treat analysis, are not useful for assessing the validity of observational studies. Accordingly, e.g. the AMNOG application templates would need to be adapted to submissions of applications based on observational studies. It is also notable that applicants report to align the reporting of their applications based on observational studies with the methodological criteria of the STROBE statement (Strengthening the Reporting of Observational Studies in Epidemiology), but the presentation of methodology and transparency of data analysis mostly do not meet the STROBE criteria.[25]

Prominent examples of FDA or EMA approval of substances that are not based on randomised studies underscore the importance and growth of new drug approval processes in the absence of evidence from RCTs.[26,27] The formulation of mandatory and more detailed criteria for the documentation of the additional benefit of innovative pharmaceuticals that are not based on randomised evidence is imperative. Moreover, applications based on observational data must be methodologically improved. In this context, attention should also be paid to prospective data collection within the framework of registries, which must be promoted for the relevant clinical pictures.

Standardised data collection is also important in terms of quality management and improves clinical research in the area of real-world evidence. At the same time, investigators should be able to expect that applications that meet the methodological and data-analytical requirements for observational studies and enable a more reliable assessment of additional benefit have a fair chance to be approved by health insurance funds.

References

[1] What is a rare disease? 2023 accessed March 7, 2023. https://go.sn.pub/NBuMaq. Accessed March 7, 2023.

[2] Julian E RA, Bussilliat P, Ruof J. Umgang mit best-verfügbarer Evidenz in der AMNOG-Nutzenbewertung von Arzneimitteln: Eine Analyse von Verfahren ohne Vorliegen einer randomisiert-kontrollierten Studie. (Dealing with best-available evidence in the AMNOG benefit assessment of drugs: an analysis of procedures without the existence of a randomized controlled trial). Unpublished manuscript. 2023.

[3] Institute for Quality and Efficiency in Healthcare (IQWiG). General methods; draft version 7.0. 2023.

[4] Institute for Quality and Efficiency in Healthcare (IQWiG). Assessment and evaluation of studies in rare diseases. 5 September 2014.

[5] Institute for Quality and Efficiency in Healthcare (IQWiG). Report No. 873 Konzepte zur Generierung versorgungsnaher Daten und deren Auswertung zum Zwecke der Nutzenbewertung von Arzneimitteln nach § 35a SGB V – Rapid Report (Concepts for the generation of healthcare-related data and their evaluation for the purpose of the benefit assessment of drugs according to § 35a SGB V - Rapid Report). Order: A19-43. Version: 1.1. 13 May 2020 [27 October 2021] https://wwwiqwigde/download/a19-43_versorgungsnahe-daten-zum-zwecke--der-nutzenbewertung_rapid-report_v1-1pdf?rev=117386 [accessed March 7, 2023]. 2020.

[6] Pardanani A. Systemic mastocytosis in adults: 2021 Update on diagnosis, risk stratification and management. Am J Hematol. 2021;96(4):508-525.

[7] Onkologie DGfHum. Opinion on the G-BA's benefit assessment of orphan drugs according to § 35a SGB V Avapritinib (new indication: advanced systemic mastocytosis). 24 July 2022.

[8] GmbH. NP. Dossier for early benefit assessment according to § 35a SGB V: Midostaurin (Rydapt®) 6 October 2017.

[9] EMA. Rydapt, INN-midostaurin - europa.eu Annex 1 Summary of the product characteristics. 2017.

[10] Blueprint Medicines (Germany) GmbH as local representative of the marketing authorization holder Blueprint Medicines (Netherlands) B. V. Dossier for the benefit assessment according to Section 35a SGB V Avapritinib (AYVAKYT®) Module 4 A. 1 April 2022.

[11] Federal Joint Committee (G-BA). Justification of the decision of the Federal Joint Committee on an amendment to the Pharmaceutical Products Directive (AM-RL): Annex XII – Benefit assessment of medicinal products with new active substances according to Section 35a SGB V Avapritinib (new indication: systemic mastocytosis, after at least 1 prior therapy). 15 September 2022.

[12] Bucher HC. Bemessung des Zusatznutzens von Arzneimitteln ohne RCT – ein Fallbeispiel. (Assessment of the added benefit of drugs without RCT – a case study) Interdisciplinary platform on benefit assessment AMNOG: Financial stabilisation - new treatment paradigms. March 2023;16:48-59.

[13] Lubke J, Schwaab J, Naumann N, et al. Superior Efficacy of Midostaurin Over Cladribine in Advanced Systemic Mastocytosis: A Registry-Based Analysis. J Clin Oncol. 2022;40(16):1783-1794.

[14] Kasamon YL, Ko CW, Subramaniam S, et al. FDA Approval Summary: Midostaurin for the Treatment of Advanced Systemic Mastocytosis. Oncologist. 2018;23(12):1511-1519.

[15] Tefferi A, Kittur J, Farrukh F, et al. Cladribine therapy for advanced and indolent systemic mastocytosis: Mayo Clinic experience in 42 consecutive cases. Br J Haematol. 2022;196(4):975-983.

[16] Munoz-Gonzalez JI, Alvarez-Twose I, Jara-Acevedo M, et al. Proposed global prognostic score for systemic mastocytosis: A retrospective prognostic modelling study. Lancet Haematol. 2021;8(3):e194-e204.

[17] Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. BMJ. 2019;367:l5657.

[18] Waernbaum I. Model misspecification and robustness in causal inference: comparing matching with doubly robust estimation. Stat Med. 2012;31(15):1572-1581.

[19] Hernán MA, Wang W, Leaf DE. Target Trial Emulation: A Framework for Causal Inference From Observational Data. JAMA. 2022;328(24):2446-2447.

[20] Hernán MA. Methods of Public Health Research - Strengthening Causal Inference from Observational Data. N Engl J Med. 2021;385(15):1345-1348.

[21] Danaei G, Rodriguez LA, Cantero OF, Logan R, Hernán MA. Observational data for comparative effectiveness research: An emulation of randomised trials of statins and primary prevention of coronary heart disease. Stat Methods Med Res. 2013;22(1):70-96.

[22] Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016;183(8):758-764.

[23] Hernán MA RJ. Causal Inference.: Boca Raton, FL: Chapman & Hall/CRC; 2016.

[24] Vanier A, Fernandez J, Kelley S, et al. Rapid access to innovative medicinal products while ensuring relevant health technology assessment. Position of the French National Authority for Health. BMJ Evid Based Med. 2023. https://go.sn.pub/gR9AUY

[25] von Elm E, Altman DG, Egger M et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-1457.

[26] Food and Drug Administration. Real World Evidence. https://wwwfdagov/science-research/science-and-research-special-topics/real--world-evidence [accessed March 8, 2023]. 2021.

[27] Concato J, Corrigan-Curay J. Real-World Evidence - Where Are We Now? N Engl J Med. 2022;386(18):1680-1682.

Quo vadis, HTA? Major discussion points with the speakers

Professor Christian Dierks | Managing Partner Dierks+Company, President of the German Society for Medical Law

Against the background of the EU HTA Regulation currently being implemented and the three presentations by Stefan Lange („EU HTA & AMNOG – Status of method development"), Bernhard Wörmann („Methodological Key Points for D & EU – View of the Professional Associations") and Sandro Gsteiger („Pain Points EU HTA from the Perspective of Health Technology Developers") reflected on the following three questions during the panel discussion:

What is the acceptable level of uncertainty in benefit assessment?

- *The law understands insecurity in the context of causality assessment for the attribution of action and liability on the one hand and for the substantiation of claims on the other. While in criminal law doubts preclude a sanction – here an „almost certain probability" is required – a „degree of certainty useful for practical life that puts a stop to reasonable doubts, admittedly without completely excluding them" is sufficient for the attribution of claims for damages.*

- *From a patient's point of view who wants to be treated with an innovative therapy, a claim exists against the social security system if there is „more in favour than against" with regard to the benefit. The Federal Constitutional Court brought this to the point in its so-called „Nicholas decision", that insured persons with a life-threatening or presumably fatal disease or with a disease that is at least comparable in terms of value, for which a generally recognised service that corresponds to the medical standard is not available, can also claim an unrecognised service if there is a not entirely remote prospect of a cure or of a noticeable positive effect on the course of the disease. Do we take this relatively low level sufficiently into account when assessing uncertainty?*

- *It was discussed in the panel that the level of acceptable uncertainty is assessed depending on the disease and context. This results in different requirements e.g. for the therapy of breast carcinoma than for orphan diseases. This is also the rationale for the privileged treatment of orphan drugs.*

Do we have the right way of dealing with potential conflicts of interest?

- *The current existing concept of conflicts of interest assessment does not provide for any selection*

Professor Christian Dierks *is a lawyer, specialist in social law, specialist in medical law, specialist in general medicine. Since 2003, he has been Professor of Health Systems Research at the Charité Berlin. Since 2011, he has represented and advised in early benefit assessment procedures. Moreover, he is a member of the European Access Academy.*

mechanisms for the experts to be involved. In order to establish a conflict of interest, it is sufficient under the regulation that the expert has an „interest" in the subject matter of the technology being assessed. Once this interest has been established, the exclusion of the expert is the only consequence currently provided for. The question is whether this system can provide sufficient expertise or whether a differentiated approach to expert selection and handling of conflicts is required.

- *This question was discussed in the panel and it was pointed out that there were sufficient possibilities to exclude „eminence-based" statements and only consider evidence. According to the author, this should be further discussed.*

Is there a need for a remuneration structure for the experts/specialist societies/patient organisations and others to be involved in the benefit assessment?

- *In view of the scarce human resources, the question arises as to whether the model of financial compensation for the input of experts, which is already practised in Germany, should be transferred to the EU level.*

- *In the panel, it was essentially confirmed that this could provide positive incentives, especially since an „excessive demand" is foreseeable. However, this was a matter for the member states.*

EU HTA & AMNOG – Status of method development

Dr Stefan Lange | Deputy Director of the Institute for Quality and Efficiency in Healthcare (IQWiG), Cologne, Germany

This article highlights the similarities and differences in specific methodological and procedural aspects between the procedure of the AMNOG (German Medicines Market Reorganisation Act) and the joint European benefit assessment („EU HTA"). Since the „bodies" of the European procedure (coordination group, subgroups) have only just been formed and various implementing acts must still be adopted on the Union side, this can only provide a picture of the status. Rough key points of a benefit assessment are comparable between the two regulatory frameworks.

Introduction

In January 2022, Regulation (EU) 2021/2282 of the European Parliament and the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU (in short: HTAR) entered into force. The regulation applies from 1 January 2025.[1] This is the first time that a joint HTA (Health Technology Assessment) by the member states of the European Union (EU) has been placed on a legal basis after three so-called Joint Actions (JA). After the expiry of the third Joint Action in September 2021, further intensive preparatory work was conducted as a service contract between the EU and a consortium of 13 HTA organisations from twelve member states (EUnetHTA 21), which were involved in the previous Joint Action to improve the conditions for the joint assessments (JCAs). EUnetHTA 21 expires on 16 September 2023.[2]

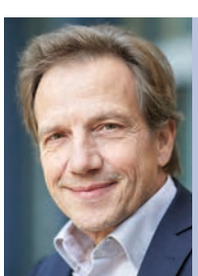
Within the framework of EUnetHTA 21, numerous methodological and procedural guidelines have been developed.[3] The difficulty was that several framework conditions have not yet been established during the contract period or have still not been established. For example, the EU Commission still must draw up so-called implementing acts (tertiary legal acts), which contain further specifications of the legal framework. In addition, the interaction between the HTAR Secretariat of the EU Commission and the „bodies" of the HTAR (coordination group, subgroups) must still be established. The coordination group – with the support of the subgroups – will be responsible to adopt the guidelines and procedures to be applied (Article 3 para. 7 HTAR). The aim is to use the preliminary work from EUnetHTA 21 as far as possible. Subsequently, examples of the methodological similarities and differences between the German (AMNOG) and the European legal framework (HTAR) will be outline.

PICO

According to the international standards, the scientific question to be answered by an HTA is determined based on the so-called PICO scheme. This means that the application situation (population), the intervention to be evaluated, a comparator intervention (comparator) and the relevant outcomes must be defined. Corresponding explanations arise (partly implicitly) in the AMNOG and in the HTAR. Section 35a para. 1 of the Social Code Book V (SGB V) states, for example: „... assessment of the additional benefit compared to the appropriate comparator therapy, ...“; and in section 2 (para. 3) of the AM-NutzenV the endpoints are clearly specified: „The benefit of a pharmaceutical within the meaning of this regulation is the patient-relevant therapeutic effect, especially the improvement of the physical condition, reduction in duration of the disease, prolongation of survival time, reduction of side-effects, as well as improvement of the quality of life.“ In the HTAR, the PICO scheme is taken up quite explicitly in Article 8(6), although it quite generally refers to „health-related outcomes“.

Very centrally, Article 8(6) of the HTAR clearly specifies that „... the scope of the assessment shall be inclusive and correspond to the needs of the member states in terms of parameters and information, data, analyses and other evidence to be provided by the health technology developer“. This means nothing else than that there may be different PICOs for different member states, which must be addressed by the pharmaceutical companies in their dossiers.

This is also found – albeit in a different context – in recital 28 of the HTAR: „(For example, the joint clinical evaluation report could include several comparators, only some of which are relevant for a certain member state)“. A process has therefore been developed in EUnetHTA 21 to describe how to develop and gather the research questions required for the dossier and assessment.[4]



Dr Stefan Lange *studied human medicine at the Heinrich Heine University in Düsseldorf from 1982 to 1989. After his internship from 1989 to 1993, he worked as assistant physician at the Medical Clinic of the Ferdinand Sauerbruch Hospital in Wuppertal. From 1993 to 2004, he worked as research associate and research assistant at the Department of Medical Informatics, Biometry and Epidemiology at the Ruhr University in Bochum. He received his doctorate in 1994 and his habilitation and Venia legendi for „Medical Biometry and Clinical Epidemiology“ in 2003. Since 2004, he has been working at the IQWiG and since 2005 he has been deputy director of the institute.*

Evidence base

Recital 35 of the HTAR states a clear preference for the evidence base: „For the conduct of the joint clinical assessment of a pharmaceutical, direct comparative clinical studies that are randomised, blinded and include a control group, and whose methodology complies with the international standards of evidence-based medicine, should preferably be considered“. This essentially corresponds to the AMNOG specifications, whereby the relevant regulations (Section 35a SGB V and AM-NutzenV) refer to „clinical trials“ or „clinical studies“ as well as registration studies.

However, both sets of regulations also allow exceptions

to the „gold standard" randomised controlled trial (RCT), as in the HTAR: „This approach should not, however, exclude from the outset available observational studies, including those based on real-world data" (recital 35 HTAR) or in the AMNOG "If there are no direct comparative studies for the new pharmaceutical versus the appropriate comparator therapy or if these do not allow sufficient conclusions about an additional benefit, available clinical studies for the appropriate comparator therapy that are suitable for an indirect comparison with the pharmaceutical with new active substances may be used" (section 5 para. 5 AM-NutzenV).

Since 2019, the G-BA has legally stipulated the requirement for a so-called post-market data collection for the early benefit assessment, which is intended to allow quantification of the additional benefit for orphan drugs and advanced therapeutic medicinal products (ATMPs) if the data situation does not yet permit this at the time of the (early) benefit assessment.[5] A rather astonishing stipulation is, however, that post-market data collection must not be randomised.[6]

Moreover, both sets of regulations have in common that the assessments „include an analysis of the scientific uncertainties as well as the robustness and limitations of the evidence (e.g. internal and external validity)" (recital 28 HTAR) or „the strength of the evidence shall be presented, taking into account the study quality, the validity of the endpoints used and the level of evidence, and an assessment shall be made of the likelihood and extent of an additional benefit" (section 5 para. 6 AM-NutzenV).

Orphan drugs

One important difference between HTAR and AMNOG is the handling of orphan drugs. Recital 24 of the HTAR expresses the expectation that „The methods for conducting joint clinical evaluations and joint scientific advice [should] be adapted to consider the specificities of new health technologies for which some data may not be readily available. This may be the case for orphan drugs, vaccines, and advanced therapy medicinal products, among others". Thus, there is no specific „orphan privilege" as in the AMNOG (although this is also only temporary after a certain sales threshold has been exceeded), namely that an additional benefit is given qua law and thus the scope of assessment is to be limited to the registration studies without specifying an appropriate comparator therapy (section 35a para. 1 SGB V). It remains to be clarified how the joint European assessment and its result can be coordinated with the German AMNOG process. In any case, post-market data collection is currently not planned at the European level.

Transferability

Another specification from ANMOG has no (at least explicit) equivalent in the HTAR: Section 5 (5a) of the AM-NutzenV provides that „When evaluating medicinal products with an authorisation for paediatric use ... the Federal Joint Committee [examines] whether an additional benefit can be recognised for patient groups or sub-indications which are covered by the marketing authorisation but which are not or not sufficiently represented in the study population and for which the marketing authorisation was granted on the basis of the transfer of evidence".

Although a guideline on the applicability of evidence has been developed within the framework of EUnetHTA 21, which could in principle also touch on such issues, it is currently limited to dealing with aspects of multiplicity,[7] which play only a minor role in assessments within the AMNOG procedure. Conversely, this means for the AMNOG procedure that it may have to be clarified how to deal with indications of multiplicity problems in joint European as-

sessments. This guideline also reveals two possible approaches to an assessment, which are fundamentally different from each other: On the one hand, the assessment on the basis of one or more individual (original) studies, taking into account the statistical-methodological approach(es) defined in these study(ies) (e.g. dealing with the multiplicity problem), and on the other hand, the assessment as a so-called evidence synthesis with its own methodological specifications (e.g. no consideration of the multiplicity problem as a rule). The latter corresponds in principle to the procedure of IQWiG and the G-BA within the framework of the AMNOG. The harmonisation of the two approaches will be a central task of the HTAR coordination group and the responsible subgroups in the coming years.

Single arm studies (unconnected networks)

A special guideline developed within the framework of EUnetHTA 21 stipulates a clear position on the significance of 1-arm studies for the case of unconnected networks (unadjusted indirect comparisons), an evidence base increasingly accepted by the European Medicines Agency (EMA) for marketing authorisation in recent years, especially for ATMPs. The guideline describes that analyses of such unadjusted indirect comparisons are based on very strong assumptions that cannot be verified in almost all practical applications. Therefore, these comparisons are highly problematic.[8] In this context, another guideline recommends conducting a so-called emulation of a target study.[9]

„Emulation of a target study" means planning a non-randomised study essentially in exactly the same way as a randomised study, but omitting the randomisation.[10] In doing so, strongly biasing moments can be reduced, for example by determining a common starting point of observation for the interventions to be compared („time zero"). The IQWiG had already referred to this possibility in its „Concepts for the generation of data close to the point of care and their evaluation for the purpose of the benefit assessment of pharmaceuticals according to § 35a SGB V".[11]

Scoping, participation during the assessment

Article 8 (6) of the HTAR stipulates that patients, clinical experts and other „relevant experts" should also be able to participate in the definition of the scope of the assessment. However, the details still have to be determined in corresponding implementing acts (Article 15 para. 1c and Article 25 para. 1b HTAR). The term „definition of the scope of the assessment" can also be understood as a so-called scoping process. Such scoping is not provided for in the AMNOG, although the G-BA determines the appropriate comparator therapy, i.e. the letter „C" in the PICO scheme (Section 35a SGB V) prior to the assessment.

Without this being stipulated in the AMNOG, the IQWiG „regularly includes medical expertise of external experts as well as the patient perspective via affected persons or patient organisations",[12] which can influence the scope of the assessment (e.g. patient-relevant outcomes important for affected persons). The EUnetHTA 21 guideline on the scoping process mentioned above describes the involvement of patients and clinical experts at both European and national level. The latter is the responsibility of the member states.[4]

In addition to scoping, Article 11(4) of the HTAR states that „patients, clinical experts and other relevant experts shall be involved in the evaluation process by being given the opportunity to contribute to the preparation of the draft reports". The details of this will also be set out in the above-mentioned implementing acts. In the framework of EUnetHTA 21, a guideline has been developed to support the involvement of patients, clinical experts and (other) stakeholders (e.g. patient representative organisations) in the assessment process.[13] This involvement is based on

specific questions raised by the assessors during the assessment. The AMNOG does not provide for the participation of these groups during the assessment, although they have the right to submit comments after the end and publication of the assessment (see also below) as well as the regular involvement of external experts at IQWiG as described above.

Fact checks, confidentiality

Another special feature of the HTAR is the possibility for the pharmaceutical companies to point out „any purely technical or factual inaccuracies" within the assessment process. Moreover, they can indicate which information they consider confidential (Article 11 para. 5). However, they are not supposed to submit comments on the evaluation results. In the past, the pharmaceutical companies were also granted the right to review the (thus preliminary) assessment reports for errors („fact check") in the joint assessments within the framework of EUnetHTA.

In EUnetHTA 21, a corresponding guideline was developed.[14] AMNOG does not provide such an intervention in the assessment, but the pharmaceutical companies have the right to submit comments to the G-BA after completion of the assessment by IQWiG (or the G-BA in the case of orphan drugs) and publication of the assessment by the G-BA, as do relevant associations, medical societies and individual experts.[15] All comments will be published after the end of the procedure.

As far as confidentiality is concerned, the regulation in the AMNOG is clearer: The dossier to be submitted by the pharmaceutical companies is to be published except for module 5, which contains e.g. study reports. The assessment by IQWiG (or the G-BA in the case of orphan drugs) is essentially based on the publishable modules 1 to 4. Especially module 4 must contain all information about methods and results. If this is not the case, pharmaceutical companies run the risk that their dossier will be considered incomplete, and a possible additional benefit will be classified as „not proven".

Conclusion

The main pillars of a benefit assessment are comparable between HTAR and AMNOG. This concerns the evidence base with the primary role of (comparative) clinical studies, the definition of the scope of the assessment based on the so-called PICO scheme and the focus on patient-relevant outcomes. Both regulations allow exceptions from the basic expectations, especially for orphan drugs and ATMPs, whereby the AMNOG additionally opens up the generation of a better evidence base with the possibility of demanding post-market data collection.

It is remarkable that the HTAR does not recognise an „orphan privilege" as specified in AMNOG. However, this privilege also has an „evaluative" element (the additional benefit is considered proven), which is explicitly not to be the subject of the European assessment (Article 9 para. 1 HTAR). A further comparison is currently not possible, as the implementing acts are still pending. Further discussions as well as substantial preparatory work in the HTAR coordination group and the subgroups are still required.

References

[1] 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. OJ L 2021/458: 1-32.

[2] EUnetHTA 21. About EUnetHTA 21 [online]. 2023 [accessed on 29 May 2023). URL: https://www.eunethta.eu/about-eunethta/.

[3] EUnetHTA 21. Joint HTA Work [online]. 2023 [access: 29 May 2023). URL: https://www.eunethta.eu/jointhtawork/.

[4] EUnetHTA 21. Practical Guideline D4.2 SCOPING PROCESS [online]. 2023 [access: 29 May 2023). URL: https://www.eunethta.eu/wp-content/uploads/2022/09/EUnetHTA-21-D4.2-practical-guideline-on-scoping-process-v1.0.pdf.

[5] Federal Ministry of Health. Act for Greater Safety in the Supply of Medicines (GSAV) Federal Law Gazette 2019; Part 1(30): 1202-1220.

[6] Federal Ministry of Health. Draft law on the reorganisation of the pharmaceutical market in Statutory Health Insurance (German Pharmaceutical Market Reorganisation Act, AMNOG) [online]. 2019 [accessed on 19 May 2023). URL: https://go.sn.pub/ESbg4x

[7] EUnetHTA 21. Practical Guideline D4.5 APPLICABILITY OF EVIDENCE – PRACTICAL GUIDELINE ON MULTIPLICITY, SUBGROUP, SENSITIVITY AND POST HOC ANALYSES [online]. 2023 [accessed on 29 May 2023). URL: https://go.sn.pub/RBC9HH

[8] EUnetHTA 21. Methods Guideline D4.3.2 DIRECT AND INDIRECT COMPARISONS [online]. 2023 [accessed on 29 May 2023). URL: https://go.sn.pub/pc2SCx

[9] EUnetHTA 21. Practical Guideline D4.6 VALIDITY OF CLINICAL STUDIES [online]. 2023 [accessed on 29 May 2023). URL:: https://go.sn.pub/H7uM9F

[10] Hernan MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. Am J Epidemiol 2016; 183(8): 758-764.

[11] Institute for Quality and Efficiency in Healthcare (IQWiG). Konzepte zur Generierung versorgungsnaher Daten und deren Auswertung zum Zwecke der Nutzenbewertung von Arzneimitteln nach § 35a SGB V – Version 1.1 (Concepts for the generation of data close to the point of care and their evaluation for the purpose of the benefit assessment of pharmaceuticals according to § 35a SGB V - Version 1.1) [online]. 13 May 2020 [accessed on 29 May 2023). (IQWiG-Reports; Volume 863). URL: https://go.sn.pub/KiQUPh

[12] Institute for Quality and Efficiency in Healthcare (IQWiG). General Methods – Version 6.1 [online]. 24 January 2022 [accessed on 29 May 2023). URL: URL: https://go.sn.pub/k62ysv

[13] EUnetHTA 21. D7.2 – GUIDANCE ON PATIENT & HEALTHCARE PROFESSIONAL INVOLVEMENT [online]. 2023 [accessed on 29 May 2023). URL: https://go.sn.pub/1RM3dg

[14] EUnetHTA 21. D7.1.2 - PROCEDURE AND FRAMEWORK FOR THE FACTUAL ACCURACY CHECK [online]. 2023 [accessed on 29 May 2023). URL: https://go.sn.pub/tgUKV0

[15] Federal Joint Committee. Rule of Procedures (7 April 2023) [online]. 2023 [accessed on 29 May 2023). URL: https://go.sn.pub/Nv4dK0

EU HTA: Key issues from an industry perspective

Dr Sandro Gsteiger | F. Hoffmann-La Roche AG

The implementation of the EU HTA Regulation is currently in full swing. One important element of this implementation is the development of specific guidelines to define the methodology of the Joint Clinical Assessment (JCA). The proposals developed by the EUnetHTA 21 consortium are a step in the right direction but need to be improved in certain areas. The proposals so far have not achieved sufficient harmonisation in the area of assessment scope and methodology in general. More transparency is needed regarding non-randomised evidence. Ultimately, the role of JCA reports needs to be clarified to produce meaningful reports with clear assessment of clinical evidence. These changes are necessary to achieve the objectives of the regulation such as promoting innovation and reducing duplication.

In less than two years, the first therapies will go through the new EU HTA process. As expected, such a major change is associated with a number of challenges as well as opportunities. The EU HTA Regulation (HTAR) sets out a certain vision: in particular, the preamble includes goals such as promoting innovation, reducing duplication, and reducing inequitable access to new therapies across Europe.[1]

For the implementation of the EU HTAR, methodological guidelines must be developed that shall apply throughout Europe and thus form the basis of the Joint Clinical Assessment (JCA) methodology. On behalf of the European Commission, the EUnetHTA 21 consortium has developed proposals for such methodological guidelines.[2] The development of a European HTA methodology is a difficult task and the

EUnetHTA 21 proposals are a step in the right direction. Naturally, the industry has a critical eye on some of these proposals.

In this article, I would like to go into more depth on three methodological areas where I believe improvements are needed, if the goals and visions of EU HTAR are to be realised: 1) the lack of harmonisation in terms of PICOs, but also in terms of methods in general, 2) the lack of openness to accepting non-randomised evidence, and 3) the role and informativeness of the JCA report.

Lack of harmonisation

PICO

The EU HTAR specifies that the joint clinical evaluation of new therapies should be conducted using four parameters: patient population, intervention, comparators, and endpoints. This so-called PICO scheme is derived in the „scoping process". The EUnetHTA 21 Guideline D4.2 presents a proposal of how this process could look like. Basi-

cally, it consists of the following steps. First, countries are asked about their needs; then duplicates are removed and, if certain PICOs are required by only one country, their necessity is clarified (to achieve some consolidation); then separate PICOs are defined per patient population and comparator and finally all endpoints are added to all PICOs.

This additive process might lead to a huge number of analyses, as van Engen et al. have shown in a (hypothetical) case study.[3] This process does not really limit the number of PICOs, so that in their example these authors obtained ten PICOs in the base case (and 14 in a sensitivity analysis). Moreover, the number of analyses is artificially inflated by applying all endpoints to all PICOs. Approximately half of the analyses identified in the case study are due to this multiplicative element of the process proposed by EUnetHTA 21.

Such a process would be difficult to manage within the planned time frames without compromising quality. These concerns do not only apply to the industry but can also be extended to the role of the evaluator/co-evaluator. Furthermore, indirect comparisons are to be expected as a rule in the EU context, which further complicates the analytical requirements. Thus, limitation to a feasible scope of evaluation oriented towards priorities and commonalities is necessary.

In addition to the operational problems, there are also methodological concerns. These result from the requirement formulated in EUnetHTA 21 Guideline D4.3.2 that separate PICOs should entail a separate evidence synthesis („In the case of different PICO questions, a different evidence synthesis for each PICO (e.g., pairwise meta-analysis or NMA) is generally required.", EUnetHTA 21 Methods Guideline D4.3.2 Direct and Indirect Comparisons. Version 1.0, 29 July 2022). Since different PICOs are defined for different comparators in the scoping process, a separate systematic literature search and evidence synthesis would have to be conducted for each comparator. On the one hand, this leads to a multiplication of searches and analyses. On the other hand, comparators for which indirect comparisons are required would not be analysed in an evidence network (e.g. in a network meta-analysis). Depending on the data situation, this can lead to inconsistency of the resulting effect estimates as well as omission of relevant indirect evidence for certain comparisons. For each patient population, all comparators must be combined in one PICO and analysed together according to the principles of evidence-based medicine. This is the only way to ensure that effect estimates are consistent at the European level.

HTA methods

The analysis of the EUnetHTA 21 proposals on the scoping process has revealed the lack of harmonisation specific to the definition of the scope of the assessment using a PICO scheme. This observation can be extended to the EUnetH-

Dr Sandro Gsteiger *studied mathematics and biology at the University of Fribourg. He received a PhD in statistics at the Swiss Federal Institute of Technology Lausanne, and MSc in HTA at the University of Glasgow. For more than 15 years, he has worked in the pharmaceutical industry in various roles, the last eight years of which in HTA, currently as Access Evidence Lead.*

TA 21 methodological guidelines more generally. The proposals of EUnetHTA 21 grant the countries far-reaching competences; many assessments are to be left to the countries (table 1). For example, countries should be able to decide on the validity of indirect comparisons themselves (Guideline D4.3.1). In my opinion, however, the assessment of the scientific validity of indirect comparisons should be a mandatory part of the joint clinical evaluation (i.e. part of the JCA).

It is clear that uncertainties can be weighted differently and thus assessments of added value can differ between countries. But the assessment of scientific validity belongs to the part that can take place on a pan-European basis – to exploit synergies, reduce duplication, and prevent unwarranted divergence in scientific assessment. An even more extreme example can be found in the same guideline (D4.3.1) in the chapter on time-to-event endpoints: in certain situations, the acceptability of the proportional hazard assumption is to be assessed by the countries themselves. The question arises as to which assessments should be made on a pan-European basis if not even the „proportional hazards" question can be conclusively decided at EU level. The situation is similar with the issue of surrogate endpoints. Admittedly, this question is much more difficult to answer. It is true that the scientific literature is carefully presented. Unfortunately, however, no attempt is made to develop a European consensus on the validation of surrogate endpoints.

Openness towards non-randomised evidence

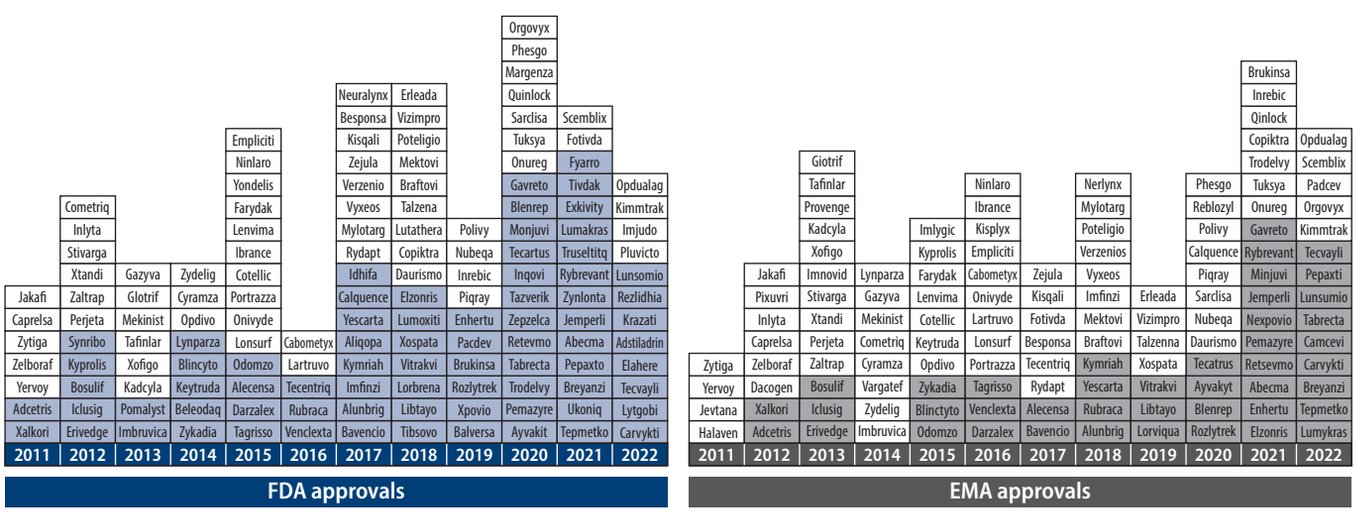
The EUnetHTA 21 methodological guidelines focus on „classical" methods and randomised evidence. These methods are also adequately presented. However, the guidelines leave little room for non-randomised evidence (table 1). At the same time, certain statements go far beyond a methodological guideline. Certain newer approaches (such as population-adjusted indirect comparisons) using single-arm studies or non-randomised evidence are viewed extremely negatively; in a sense, the methods are prejudged as unreliable and of little value (for HTA).

This extreme attitude contrasts sharply with the use of such data in the regulatory field. For example, an analysis of all FDA and EMA approvals in oncology over the last decade demonstrated a clear increase in approvals based on single-arm studies (figure 1, which includes so-called „conditional/accelerated approvals" where randomised evidence was submitted later). While this trend may not necessarily continue, it is clear that single-arm studies and non-randomised evidence are a reality in the regulatory environment.

In general, there is a differentiation away from a binary classification into „randomised versus non-randomised" towards a broad spectrum of study designs; e.g. randomised studies can be supplemented with pragmatic elements, or the control group of a randomised study is reduced in size and enriched with external controls, up to single-arm studies in which the control group is based entirely on external data.[4]

This openness is also desirable for the HTA field, as a way of dealing with different types of evidence and potentially greater uncertainty has to be found, especially due to accelerated approval procedures.[5] The scientific literature actively discusses such approaches. To mention only a small selection, the review article on external controls by Lambert et al.[6] the discussion of target trial emulation in the HTA field by authors in connection with the English National Institute of Health and Care Excellence (NICE),[7] as well as the discussion of the position of the French Haute Autorité de Santé (HAS) regarding non-randomised data by Vanier et al.[8]

Approvals (FDA and EMA) in oncology since 2011



Source: F. Hoffmann-La Roche AG

Figure 1: Analysis of all FDA and EMA approvals in oncology over the past decade reveals a clear increase in approvals based on single-arm studies (the coloured boxes show the proportion of single-arm/non-controlled studies).

The authors of HAS explicitly mention that in exceptional cases randomised trials may not be the optimal solution and that in these cases industry should discuss evidence generation plans with HTA authorities at an early stage in the Joint Scientific Consultation (JSC). This view is also desirable for the future EU HTA methodology. Randomised data are rightly considered the „gold standard". Nevertheless, new therapeutic approaches may be associated with other types of evidence. In certain cases, randomised trials are not always possible or the best solution. In the development of therapies for rare diseases, with increasing personalisation such as in precision oncology, and in curative approaches or therapies with extremely long observation periods, iterative processes and non-randomised evidence will become more important in the future.

Finally, it should not be forgotten that in the last 30 years enormous progress has been made in the area of availability, quality, and correct use of non-randomised data. Epidemiology and biostatistics have undergone a profound methodological development in the field of causal inference.[9] A general rejection of non-randomised data negates these results and is therefore not based on the latest scientific knowledge.

Ultimately, epidemiology and HTA share the objective of correctly quantifying causal effects. This is also possible with non-randomised evidence, even if this requires more assumptions and their plausibility can be difficult to establish. Nevertheless, we should have this tool at our disposal. Instead of a general rejection, high standards should be demanded.

Excerpts from the EUnetHTA 21-Guidelines that should be improved

Problem area	EUnetHTA 21 Guideline	Quote
Harmonisation	D4.3.1[a]	"Each MS should be enabled to decide on the validity of direct or indirect treatment comparisons itself."
	D4.3.1[a]	"Substantiating the Proportional Hazards assumption without such evidence might be possible in some cases, but the acceptance is then at the discretion of the MSs."
	D4.3.2[b]	"We recognise that there is an element of subjectivity in the assessment of many assumptions and that decisions may vary between member states."
	D4.5[c]	"The acceptability of sensitivity analyses is subject to member state differences in interpretation of their relevance within their respective decision-making process."
Non randomised evidence	D4.3.1[a]	"By describing these methods here, we are not endorsing them, and once again reiterate that estimates arising from unanchored ITCs are unreliable."
	D4.3.1[a]	"The requirement of all confounders and effect modifiers being measured is unlikely to be met, given that unknown modifiers and confounders are assumed to be always present."
	D4.6[d]	"In the context of HTA, uncontrolled clinical trials are of very limited value for estimating treatment effectiveness."
JCA Reports	D4.5[c]	"Effect measures should not be specified by Member States. [...] If a Member State still wants to specify an effect measure, the wording should follow this template [...]"
	D4.6[d]	"Similarly, the clinical relevance of an effect size [...] needs to be judged at the national context."

Source:
[a] EUnetHTA 21 – Individual Practical Guideline Document D4.3.1: Direct and Indirect Comparisons. Version 1.0, 16.12.2022. https://www.eunethta.eu/d4-3/
[b] EUnetHTA 21 – Methods Guideline D4.3.2: Direct and Indirect Comparisons. Version 1.0, 29.07.2022. https://www.eunethta.eu/d4-3/
[c] EUnetHTA 21 – Individual Practical Guideline Document D4.5: Applicability of Evidence – Practical Guideline on Multiplicity, Subgroup, Sensitivity and Post Hoc Analyses. https://www.eunethta.eu/d4-5/
[d] EUnetHTA 21 – Individual Practical Guideline Document D4.6: Validity of Clinical Studies. https://www.eunethta.eu/d4-6/

Table 1: The EUnetHTA 21 proposals give the impression that any weighing belongs to the competence of the countries. However, it is certainly intended to be judged, but not evaluated, at European level.

Role and significance of the JCA report

The third issue I would like to address is the role of joint clinical judgement and the resulting JCA report. The EUnetHTA 21 proposals give the impression that any consideration belongs to the competence of the countries (table 1). This stance appears to be grounded in the EU HTAR, which states in Article 9 that JCA reports „shall not contain value judgements or conclusions on the overall clinical added value of the evaluated health technology".[1]

This raises the fundamental question of the distinction between the scientific assessment and the evaluation of the added benefit, the so-called „appraisal". The terms assessment and appraisal are not uniformly defined in the literature (table 2). However, the examples given show that it is ultimately a matter of separating the scientific assessment of the evidence – which should be as objective as possible – and making a value judgement. The latter must also consider the context, social preferences, etc. in addition to the evidence. This separation does not mean that no considerations can or should take place in the assessment. But scientific considerations are made here: has all relevant evidence been systematically identified and analysed according to the latest standards? Are the assumptions plausible and adequately justified? Are the methods adequate for the given research question and evidence etc.? This also entails clear conclusions. It is certainly intended to be judged, but not evaluated, at European level. This common judgement regarding clinical evidence is necessary to establish a consistent basis for decisions in the member countries. This common basis should include clear statements regarding scientific validity and clinical relevance.

What do we actually want?

As the „HTA community" we should ask ourselves what we actually want, if the implementation of the EU HTAR is to be successful. In the spirit of a constructive dialogue, I would like to outline on five points that seem particularly important to me.

- **1. Development of a consolidated EU PICO – focus on commonalities**

The scope of the evaluation will significantly influence the feasibility and quality of the joint clinical evaluation. A certain amount of pragmatism will be necessary when creating the European PICO, especially regarding comparators and endpoints. The European PICO should focus on commonalities. Specific needs of individual countries should remain local and reasonable. Only then will the simplification and increased efficiency of HTA processes at the European level that shall be achieved with the EU HTAR.

- **2. Development of a true pan-European HTA methodology (harmonisation)**

In a statement, the German Pharmaceutical Industry Association (BPI) and the German Association of Research-Based Pharmaceutical Companies (vfa) aptly described the EUnetHTA 21 proposals as „a mere amalgamation of national practices".[10] This will leave today's fragmentation in place and may even increase complexity if, e.g. different locally preferred analytical methods with all desired endpoints are combined (i.e. if local desires multiply each other).

Scientific principles, however, should be able to be defined and standardised across countries. Thus, a genuine attempt to consolidate European HTA methodology should be sought. On the one hand, this requires the willingness to make compromises. On the other hand, and arguably more importantly, this requires clarification of the fundamental principles and concepts that should characterise European HTA as science. For example, such a principle is the issue of effect estimation versus hypothesis testing (so-

Definitions of "Assessment" and "Appraisal" in literature

Source	Assessment	Appraisal
HTA Glossary.net http://htaglossary.net	A scientific process used to describe and analyse the properties of a health technology—its safety, efficacy, feasibility and indications for use, cost and cost-effectiveness, as well as social, economic and ethical consequences.	No definition
EUnetHTA	Technical and scientific assessment	Valuation of the assessment results that supports decision-making
EFPIA	Factual relative effectiveness assessment	Translation of the factual evidence assessment into an added therapeutic value rating
EUPATI	Synthesis and critical review of scientific evidence	Advice or recommendation considering the assessment in light of wider factors related to the local context
NICE	Scientific process of review of clinical and economic evidence of new and existing medicines and treatments	Recommendation on the use of new and existing medicines and treatments within the NHS
Sandman and Heintz, 2014	Action of evaluating relevant aspects of the technology to form a basis for decision	Implies some form of recommendation about the implementation of the technology, based on the assessment.
Angelis et al. 2018	Assessment of evidence conducted by technical groups	Appraisal of the assessed evidence from an expert committee that is producing reimbursement and coverage recommendation(s) for the final decision body, which can be either the payer, or the HTA agency itself. "special considerations/social value judgements applied [are] in the appraisal phase"
Beletsi et al., 2018	The assessment report is prepared either by internal staff or by external academic organizations on the basis of the dossier submitted by the applicant	The appraisal is done by committees or boards integrated within the HTA organization or by the decision-making body
	In more "recent adopters" of HTA, the concepts of assessment and appraisal are intertwined and are mainly based on the review of the evidence provided by the applicant.	
Wiesława et al. 2019	Review and quality rating of evidence that is guided by well-developed scholarly standards	Collective judgment by committee members about the clinical benefit and value for money of the therapy based on the considered evidence package

Source: F. Hoffmann-La Roche AG

Table 2: Assessment and appraisal are not consistently defined in the literature. The separation of the two elements does not mean that no weighing can and should take place in assessment.

metimes described in the literature as „learning versus confirming"). The central goal of HTA is the correct quantification of causal effects. This means that HTA methodology should focus on effect estimation approaches. Test problems belong in the field of authorisation, and thus in the field of action of regulatory authorities such as the EMA.

Furthermore, it will be important to find the balance between flexibility and predictability. European HTA methodology must be open to innovative methods - properly applied, at the right time. Therefore, context-specific factors must be considered. Not all therapeutic areas must be

treated in the same way; specific product types each present their own challenges. Therefore, rigid regulations regarding evidence and methodology will not be helpful. At the same time, clear principles should apply. However, their implementation must not be based on rigid algorithms, but on a case-by-case basis including technical and medical expertise. Admittedly, this balancing act is not easy.

- **3. Meaningful JCA reports with clear scientific judgements**

JCA reports should contain clear scientific judgements. A mere listing of point estimates and confidence intervals will not be helpful. This requires clarity about what should be part of the scientific assessment (assessment) and when the benefit assessment (appraisal) begins. For example, assessing the scientific validity of the evidence and characterising and quantifying the uncertainty associated with an effect estimate is part of the assessment. Whether and how this uncertainty affects the value of the therapy and ultimately its reimbursement is then part of the appraisal, which may well differ between countries because, e.g. risk taking, value of innovation etc. reflect social attitudes that may differ.

- **4. Sufficient capacity, especially for joint scientific advice**

The importance of joint scientific advice (JSC) is undisputed. At the same time, the necessary capacity does not seem to be available at the moment, and the current planning is insufficient to cover the expected need for sufficient JSCs. The necessary capacities must be available in good time and on a broad basis. Justified doubts as to whether this will be achieved are not only expressed by the industry.

The other elements of the EU HTA process also need sufficient capacity. In particular, the role of assessor/co-assessor is both demanding and burdensome. Unfortunately, at this stage there are very large differences within European countries in terms of HTA knowledge and capacity. Member countries have a duty to deploy the necessary resources in a timely manner so as not to jeopardise the implementation of the EU HTAR.

- **5. Goal-oriented and meaningful participation of all stakeholders (including industry)**

Ultimately, a change as complex as the creation of an EU HTA process requires the involvement of all stakeholders. Patient organisations, medical societies, HTA authorities, academia, and industry each bring not only different views but also specific expertise. Each group can provide valuable input and thus improve the quality, practicality, and acceptability of the implementation of the EU HTAR.

Conclusion

After years of voluntary cooperation, the EU HTAR offers a unique opportunity to establish a binding European HTA structure. The focus is justifiably on the clinical dimension, while the other elements of HTA (such as economic evaluation) remain local. This can reduce the current fragmentation and inconsistency, increase efficiency, which promotes innovation.

In order to realise the benefits of EU HTAR, a European perspective is necessary. Existing (and often well-functioning) systems need to be adapted. If this is done reluctantly, failure is quite possible. Therefore, this implementation must be understood as a further development.

There is an opportunity for Europe to position itself positively and define a unified HTA methodology with meaningful, pragmatic standards. Development plans in the in-

dustry are still significantly shaped by regulatory needs. EU HTA regulation can help to clarify the necessary evidence for HTA systems and thus for better decisions in medical care at an early stage and consistently for Europe. Such an opportunity seems „too big to fail" and we should not miss it – together as the „HTA community".

Acknowledgements

I would like to thank following Roche colleagues: Maria-Joao Garcia (for providing table 2), Jeff Hille (for providing figure 1), Jutta Scherer, Vanessa Schaub, and Jan Daniels-Trautner for their valuable support. Moreover, I thank Sebastian Werner (vfa) for valuable comments and discussions.

References

[1] European Commission (EC). 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 (Text with EEA relevance). OJ L vol. 458 (2021).

[2] Services – EUnetHTA. https://www.eunethta.eu/jointhtawork/ (2021).

[3] van Engen, A., Kruger, R., Ryan, J. & Wagner, P. HTA97 Impact of Additive PICOs in a European Joint Health Technology Assessment. a Hypothetical Case Study in Lung Cancer. Value Health 25, S315 (2022).

[4] Concato, J. & Corrigan-Curay, J. Real-World Evidence – Where Are We Now? N. Engl. J. Med. 386, 1680-1682 (2022).

[5] Facey, K. M., Rannanheimo, P., Batchelor, L., Borchardt, M. & Cock, J. de. Real-world evidence to support Payer/HTA decisions about highly innovative technologies in the EU – actions for stakeholders. Int. J. Technol. Assess. Health Care 36, 459-468 (2020).

[6] Lambert, J., Dr et al. Enriching single-arm clinical trials with external controls: possibilities and pitfalls. Blood Adv. bloodadvances.2022009167 (2022) doi:10.1182/bloodadvances.2022009167.

[7] Gomes, M. et al. Target Trial Emulation for Transparent and Robust Estimation of Treatment Effects for Health Technology Assessment Using Real-World Data: Opportunities and Challenges. PharmacoEconomics 40, 577–586 (2022).

[8] Vanier, A. et al. Rapid access to innovative medicinal products while ensuring relevant health technology assessment. Position of the French National Authority for Health. BMJ Evid.-Based Med. (2023) doi:10.1136/bmjebm-2022-112091.

[9] Hernan, M. A. & Robins, James M. Causal Inference. What If. (CRC Press, 2022).

[10] VFA. Umsetzung der EU-HTA-Verordnung benötigt Richtungskorrektur. https://go.sn.pub/Zo7s43

Joint Clinical Assessment of new pharmaceuticals: Challenges for the professional societies

Professor Bernhard Wörmann | German Society for Haematology and Medical Oncology (DGHO) and Division of Haematology, Oncology, and Tumour Immunology at the Virchow Campus of the Charité Universitätsmedizin Berlin

The transfer of Health Technology Assessment (HTA) of new pharmaceuticals from the national to the EU level poses challenges for the scientific medical societies. The planned start of the Joint Clinical Assessment (JCA) for oncology products and orphan drugs would currently affect more than half of the new registrations and new market launches in Germany. The JCA requires the presentation of the current state of care in the EU and the individual member states, especially with regard to: therapeutic standard, subgroups / subpopulations, and endpoints. There is no European Association of the Scientific Medical Societies (AWMF) at European level. Also, standardised processes for high-quality and regularly updated guidelines have only been established in a few specialties at EU level. In the next 18 months, structures analogous to the German AMNOG process should be established that enable joint, timely and comprehensive opinions of all EU member states in the context of the assessment of new medicinal products.

Introduction

Pharmaceuticals are among the central tools in the prophylaxis and therapy of diseases. Their importance has increased continuously in recent decades. The availability and use of new pharmaceuticals are controlled via different access routes:

- Marketing authorisation (EU
- Market introduction and marketing (national)
- Early benefit assessment and pricing
- Guidelines (recommendations for action) (national, EU, global).

This process is illustrated in figure 1.

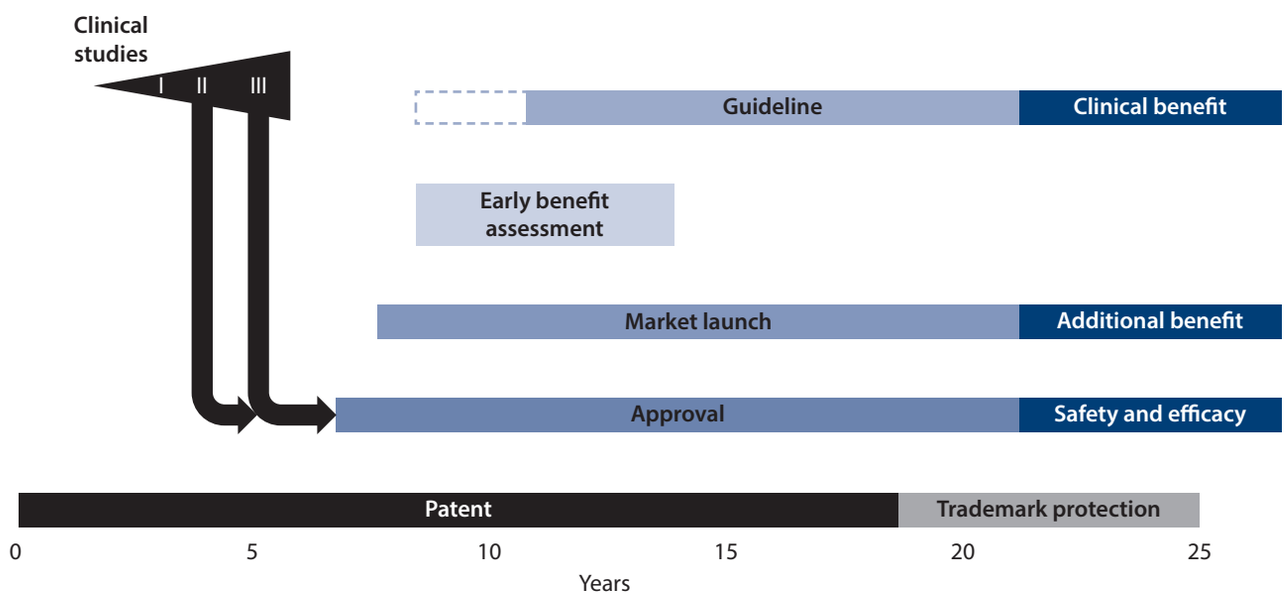
Although the same data from the pivotal clinical trials are the basis of these processes, the results are different. Discrepancies are mainly due to the intention-triggered methodology used in each case. Diverging results, e.g. between guidelines and marketing authorisation or between guidelines and health technology assessment, can enrich the critical appraisal. In the worst case, they can lead to misuse of pharmaceuticals. „Misuse“ is defined here as the use of a pharmaceutical for the wrong indication, but especially as non-use for the correct indication.

In Germany, national structures of cooperation between guidelines and the HTA process have been established over the last ten years. The intended shift of the early benefit assessment to the EU level is an opportunity to expand this experience. However, it also involves risks and poses new challenges for the professional societies.

Guidelines in Germany

In Germany, the preparation of guideline recommendations has become one of the central tasks of scientific medical societies over the last three decades. In healthcare, they form the bridge between the rapidly increasing external evidence and the individual patient situation. In Germany,

Access to new pharmaceuticals in Germany



Source: Own presentation

Figure 1: In Germany, structures of cooperation between guidelines and the HTA process have been established over the last ten years. The shift to the EU level brings opportunities and risks.

Professor Bernhard Wörmann *works as a physician specialising in internal medicine, haematology, and internal oncology with additional qualification in palliative care. Since 2010, he has been Medical Director of the German Society for Haematology and Medical Oncology (DGHO) and since 2015 he has been Chairman of the commission „Benefit assessment of pharmaceuticals" of the AWMF. He works at the Outpatient Health Centre and Medical Clinic of the Virchow Campus of the Charité Universitätsmedizin Berlin with a focus on haematology, oncology, and tumour immunology.*

the Council of Experts for Concerted Action in Health Care addressed the development of recommendations for action in 1995. Following this, the German Medical Association defined guidelines as „systematically developed decision-making aids on appropriate procedures, which leave the physician a scope for decision-making and corridors of action from which deviations may be made in justified individual cases".[1]

The Association of the Scientific Medical Societies (AWMF) has made the coordination and publication of guidelines one of its central tasks since 1995. The AWMF defined its own quality hierarchy for German-language guidelines, ascending from S1, S2k, S2e to S3.[2]. Figure 2 shows the current status of AWMF guidelines as of 1 November 2022.

The light blue bars represent guidelines in the S1 category, the medium blue bars S2 guidelines and the dark blue bars S3 guidelines. This shows a continuous trend towards methodologically higher-quality guidelines, whose total number in November 2022 was >500 in November 2022.

The preparation of these guidelines is time-consuming. Oncology has a special position because the process of guideline development is funded by the German Cancer Aid. Since 2020, the G-BA has been filling the gap for the other specialties with funds from the Innovation Fund.[3] Other problems such as the high time expenditure and the long times until the publication of new guidelines or their updating have not been solved yet. Here, concise guidelines such as the ONKOPEDIA portal for oncology and haematology have taken on an important role in the provision of care.[4] The methodological basis for the production of guidelines by scientific professional societies has been developed since 2004 by the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) platform. The aim of GRADE is to combine evidence assessment with the derivation of recommendations in clinical guidelines. Since 2004, an international group of experts has published a comprehensive system on the various contents of quality assessment, from evidence profiles to the various aspects of outcome bias to the preparation of summaries.[5, 6] In its entirety and conceptual stringency, GRADE provides a suitable platform for the uniform assessment of the quality of clinical studies.

Guidelines in Europe

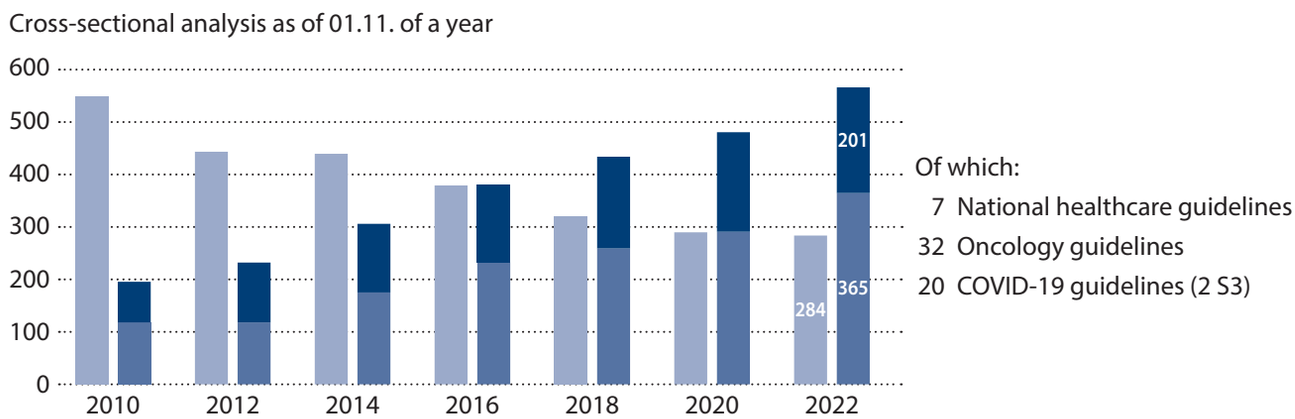
GRADE is also the basis for guidelines at the European level. Nevertheless, guideline development is much more heterogeneous here than in Germany. This has organisational, but also content-related and conceptual reasons.

Organisational: There is no European AWMF. A process of comprehensive guideline development and updating has only been established in relatively few specialities. An outstanding example of successful cooperation at the EU level are the guidelines of the European Society of Cardiology (ESC).[7] They are so up-to-date and of such high quality that the German guidelines in cardiology are completely based on the European guidelines.[8]

Medical oncology is another exceptional example. Here, the European Society of Medical Oncology (ESMO) has developed its own clinical trial assessment project.[9] The ESMO Magnitude of Clinical Benefit Scale (ESMO MCBS) provides a timely assessment of all new pharmaceuticals based on the registration studies from a clinical point of view. Another positive example are the guidelines in urology by the European Association of Urology (EAUU).[10]

In addition, there is a wealth of European guidelines on individual topics that are not listed here. The guidelines are often well published and have undergone an additional

Status of guidelines of the AWMF 2023



Source: Own presentation

Figure 2: The AWMF defined its own quality hierarchy for German-language guidelines, ascending from S1, S2k, S2e to S3 - here the current status of AWMF guidelines as of 1 November 2022.

peer review process. In case of such individual actions, particular attention should be paid to transparency with regard to possible conflicts of interest.

Content: A basic conflict in moving guidelines from the national to the European level is the definition of the claim between:

- Lowest common denominator
- State of the art.

The lowest common denominator takes into account the current state of care in both diagnostics and therapy. This can be reflected in European guidelines in that evidence-based recommendations are not included if the respective methodology or the respective pharmaceutical is not available in all countries. In practice, for example, methods of modern imaging such as MRI or PET in diagnostics or pharmaceuticals approved by the EMA in therapy may be affected. The vast majority of guidelines are based on the state of knowledge and claim that the national standard of care is based on the guidelines, not vice versa.

From the dominance of individual experts to the art of consensus building

Within the framework of the processes for the preparation of guidelines, a profound structural change has taken place in the professional societies over the last 25 years. The formerly established, dominating position of individual experts (here correctly negated because the vast majority of them were men) has been replaced by guideline commissions with sometimes more than 50 experts. These are recruited from all medical fields, but also from all areas relevant to health care, which deal with the respective indication or are affected by it. The precursor to this was the establishment of local tumour conferences in oncology in the mid-1990s. Here the culture of evidence-based argumentation was practised, but also the face-saving and

even image-enhancing art of consensus-building. Of course, patient self-help organisations are also involved in the preparation of the guidelines.

Here, the scientific medical societies are one step ahead in terms of structure and willingness to discuss than some regulatory authorities, but also than individual HTA institutions.

National content for the Joint Clinical Assessment

The most important role of the scientific medical associations in the now planned Joint Clinical Assessment (JCA) of new pharmaceuticals is to ensure that the respective national standard of care is taken into account. This information must be included in the dossier of the pharmaceutical company in order to enable the national appraisal of the new pharmaceutical later on. The formal underlying, so-called PICO scheme corresponds to the procedure for the preparation of guidelines. In terms of content, these points are particularly relevant for the early benefit assessment:

- Comparator
- Subgroups
- Aim of the therapy.

Comparator: The comparator reflects the current standard of care. Occasional concerns that dossiers will in future contain as many comparators as EU member states are not well founded. However, it is to be expected that there will be several comparators, not all of which correspond to the control arm of the respective pivotal study. Figures 3 and 4 show two current innovations:

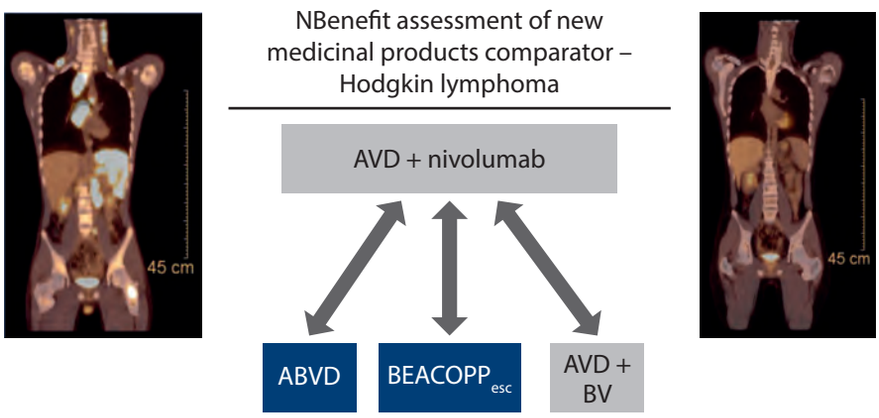
The registration study of the immune checkpoint inhibitor nivolumab in first-line advanced Hodgkin's lymphoma compares AVD-nivolumab versus AVD-brentuximab vedotin (highlighted in blue in figure 3).[11] This does not correspond to the standard of care in Germany, where the eBEACOPP regimen, rather than AVD-brentuximab vedotin, is extensively used. In many other European countries, neither AVD-brentuximab vedotin nor eBEACOPP but the conventional ABVD regimen is the standard. In a current fictitious dossier for the JCA, three comparators would be listed (figure 4).

For gene therapy with valoctocogen roxaparvovec for haemophilia A, there was no comparator arm in the pivotal study, as is regularly the case in pivotal studies for new pharmaceuticals for the prophylaxis and therapy of haemophilia. For many years, plasmatic or recombinant factor VIII preparations were the standard.[12] In many countries, half-life-extended FVIII preparations have become established in recent years. With the same efficacy, they allow longer application intervals of weekly to four-weekly. Moreover, with the antibody emicizumab, a preparation is now available that can also be used in patients with inhibitory antibodies due to its different mechanism of action. Patients also prefer emicizumab because of its subcutaneous injection (in contrast to the intravenous administration of the FVIII preparations). Again, in a current notional dossier for the JCA, three comparators would be listed.

Subgroups: Not all national health systems in the EU use new pharmaceuticals in all patients but limit their use to defined patient groups. Conceivable are certain stages, e.g. in the adjuvant therapy of breast or lung cancer, or upper age limits. In some countries there are also legal requirements, e.g. the German AMNOG.[13] Explicitly mentioned parameters are e.g. gender, age, disease severity, or stage. These specifications for the national appraisal must also be taken into account in the dossier.

Endpoints: National HTA procedures may deviate from international standards with regard to endpoints. One exam-

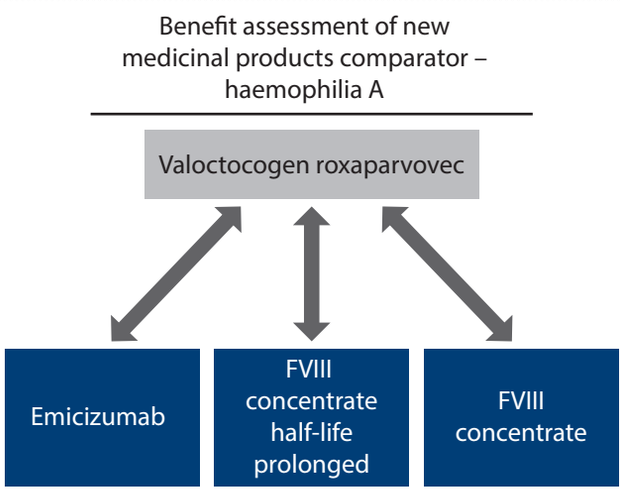
Comparator for the evaluation of nivolumab in advanced Hodgkin lymphoma



Source: Own presentation

Figure 3: The pivotal study of the immune checkpoint inhibitor nivolumab in first-line advanced Hodgkin lymphoma comparing AVD-nivolumab versus AVD-brentuximab vedotin.

Comparator for the evaluation of Valoctocogen roxaparvovec in haemophilia A



Source: Own presentation

Figure 4: Three comparators would be listed in a current notional dossier for the JCA.

ple is the handling of progression-free survival. Based on an early methods paper by the Institute for Quality and Efficiency in Health Care (IQWiG) in Cologne, this endpoint is not relevant for use in the AMNOG process. However, in oncology, for example, it is regularly the primary study endpoint. Such a national idiosyncrasy must also be taken into account in the dossier for the JCA.

Organisation of statements for the Joint Clinical Assessment

Based on the German experience over the last ten years, the establishment of functional, indication-related expert teams is a prerequisite for handling the HTA request in the context of the early benefit assessment of a new pharmaceutical. Figure 5 shows a possible process flow. The model provides for a central office in which the comments are coordinated. Experience has shown that the quality of the comments and the adherence to deadlines depend signifi-

Model of organisation of scientific medical opinions for the JCA at EU level

Source: Own presentation

Figure 5: The establishment of functional, indication-related expert teams is the prerequisite for managing the HTA request in the context of the early benefit assessment of new pharmaceuticals.

cantly on this professionalised coordinating body. It receives requests and prepares the draft of an opinion. This goes to the national expert panels with the request for focused entry of the relevant, national points in the PICO scheme (see above). This feedback is then summarised and sent as a joint EU opinion.

Perspectiv

The establishment of a European opinion procedure of scientific medical societies first for oncology products and then for orphan drugs is costly. However, it can also be a further – perhaps even the decisive – trigger for the establishment of high-quality, European guidelines. Then the European HTA process, which is currently experienced by many as an additional burden, would become a project that shapes the future.

References

[1] German Medical Association: „Verbindlichkeit von Richtlinien, Leitlinien, Empfehlungen und Stellungnahmen." (Binding force of directives, guidelines, and statements). www.bundesaerztekammer.de/page.asp?his=0.7

[2] Rules and regulations | Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V. (awmf.org)

[3] Funding announcement (g-ba.de)

[4] Guidelines – Onkopedia

[5] GRADE guidelines 1: Guyatt G, Oxman AD, Akl E et al.: GRADE guidelines 1: introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 64:383-394, 2013. DOI: 10.1016/j.jclinepi.2010.04.026

[6] GRADE guidelines 3: Balshem H, Helfand M, Schünemann HJ et al.: GRADE guidelines 3: rating the quality of evidence. J Clin Epidemiol 64:401-406, 2013. DOI: 10.1016/j.jclinepi.2010.07.015

[7] ESC Clinical Practice Guidelines (escardio.org)

[8] Guidelines: of the German Society of Cardiology - Cardiovascular Research e.V. (dgk.org)

[9] ESMO-MCBS for Solid Tumours | ESMO

[10] EAU Guidelines – Uroweb

[11] Herrera A et al.: SWOG S1826, a randomized study of nivolumab(N)-AVD versus brentuximab vedotin (BV)-AVD in advanced stage (AS) classic Hodgkin lymphoma (HL). ASCO Abstract LBA4, 2023), Program Guide – ASCO Meeting Program Guid

[12] Benefit assessment procedure for the active substance valoctocogen roxaparvovec (haemophilia A) – Federal Joint Committee (g-ba.de

[13] German Pharmaceutical Market Reorganisation Act (AMNOG), Federal Law Gazette Part I dated 27 December 2010. https://go.sn.pub/kTPilv

EU-HTA: The rules of the game for assessment standards and procedures are just evolving

Dr Florian Staeck

With its entry into force on 12 January 2025, the project of a European Benefit Assessment (EU HTA) is approaching, but many questions remain unanswered regarding timelines and the content-related scope of the future Joint Clinical Assessments (JCA). As a result, it has not yet been clarified e.g. what the concrete consequences will be for the national early benefit assessment procedure according to AMNOG.

It is true that the EU regulation demands an „inclusive" scope of assessment, which according to the legal text has many parallels to the AMNOG procedure. However, especially industry representatives are convinced that too little harmonisation of the heterogeneous national procedures is achieved in the previous draft guidelines, in which methodological questions of EU HTA are discussed. In this respect, further preparations in the remaining year and a half or so will be of significant importance for a successful start of the European benefit assessment from 2025. The participants of the 17th meeting of the Interdisciplinary Platform for Benefit Assessment in Berlin on 17/18 March 2023 were convinced of this.

The following issues were discussed at the meeting:

Previous preparatory work by EUnetHTA-21 and the European Commission

The methodological preparatory work in the so-called Preparatory Phase is mainly carried out by EUNetHTA21, a consortium of 13 EU Member States. Other important activities during this phase are primarily coordinated by the European Commission. Among other things, this involves the establishment of a stakeholder network and an IT platform on which documents can later be uploaded and downloaded within the framework of the JCA. Participants were astonished that until March 2023 the coordination group, which will centrally coordinate the future HTA assessment as an important unifying body of the member states, had only met twice. This frequency would have to be drastically increased in view of the tasks to be accomplished, they said. In addition, the associated secretariat, which is located at the Directorate-General for Health of the EU Commission, should provide administrative and technical support, but currently only has a headcount of 3.5 positions, it was reported. Participants unanimously noted that that was a very tight staffing which was predictably insufficient.

It was also described as unclear to what extent the „deliverables" currently being developed by EUnetHTA21, in which concretisations regarding methodological questions and the JCA are being worked out, would be affected by the Implementing Acts, which would still have to be drawn up by the EU Commission. In case of these supporting legal acts, which are provided for in the EU Regulation itself, it was currently still debatable to what depth of detail specifications would be made there. This in turn could have repercussions on the methodological proposals developed by EUnetHTA. In all this, the timetable was already tight, as the time required for the implementation of Implementing Acts is usually 12 to 18 months, it was reported.

Timing of the EU HTA and consequences for the AMNOG procedure

At present, the exact timeline of the European benefit assessment was still associated with great uncertainty. This concerns the question of when the JCA report was expected to be available and which temporal adjustments were associated with it in the AMNOG procedure, it was reported. Currently, there were only two fixed time requirements

based on the EU HTA regulation: On the one hand, the manufacturer's dossier should be submitted 45 days before the so-called positive opinion of the EMA.

On the other hand, the JCA would have to be submitted 30 days after the approval was granted. However, on the one hand, the Positive Opinion was a „moving target", on the other hand, the maximum of 67 days between the Positive Opinion of the Committee for Medicinal Products for Human Use (CHMP) and the final authorisation by the European Commission was often not reached. It was pointed out that this could lead to further uncertainties in the course of the parallel HTA processes.

For the G-BA, this created the new situation of having to consider a benefit assessment report that was developed in parallel to the approval. Until now, the G-BA had only started the benefit assessment once the approval was granted.

Further challenges in the timing and conflicts for submission dates in the national procedure could arise if the indication originally applied for by the manufacturer deviates from the final indication of the EMA. In a study of 50 procedures that passed the G-BA procedure in 2020/21, significant differences were found between the requested and final indication in 10 % of the cases, and in most cases the EMA complained that the indication was too broad. The corresponding concerns of the EMA, however, were almost always visible in the Day 120 and Day 180 Reports – two points in the approval process at which the „clock is stopped". In this respect, manufacturers could usually estimate the expected decision of the approval authority well, participants said. However, frictions would arise in the case of an accelerated approval. In that case, the 45-day deadline specified in the regulation would no longer be manageable, participants outlined.

The still uneven schedule generates further uncertainty in the process in case of orphan drugs. Also, the European HTA procedure would start although the approval process was not yet completed. Since the orphan designation is only confirmed by the EMA within the framework of the positive opinion, it remained unclear for orphan drugs until the time of the positive opinion whether the EU HTA procedure will be applicable in individual cases before 2030.

Participants pointed out that the practicability of the timelines was currently still being investigated. However, a far-reaching readjustment would presumably only be possible in the review process, which is envisaged in the regulation from 2028.

Methodological questions of the European benefit assessment that have not yet been clarified and/or are controversial

1. Number of PICO schemes to be expected: Many discussions at the platform meeting revolved around the process of defining the questions for the benefit assessment. A special feature in the EU HTA is, among other things, that this is to be done in the scoping process, whereas in the AMNOG procedure this is done in the context of the consultation by the G-BA. Participants expressed the fear that this could result in a large number of PICOs from the EU member states. This would also mean that endpoints or comparative therapies would not be „consolidated", but only listed additively.

Against this background, several participants expressly welcomed the fact that test runs are currently being carried out by EUnetHTA21 as part of the development of the scoping guideline. The MOCK-PICOs developed in this context were aimed at simulating a consolidation of PICOs. It was already considered a „milestone" if there were four PI-

COs at the end of this process, participants explained.

The goal would have to be to obtain data sets that are relevant for all member states. This was probably a major challenge, especially for application areas that involve a very heterogeneous patient population, they outlined. Participants familiar with the test runs reported that it was a „learning curve" in understanding and approaching the data together. It was not (yet) a harmonisation, but merely a merging of perspectives.

It was countered that a mere amalgamation of methods of the member states could not be effective. Instead, a consolidated „EU-PICO" based on a pan-European HTA methodology should be developed. Otherwise, there could be a multiplication of analyses, which could produce inconsistent analyses, e.g. regarding the effect estimates. If this consolidation was not possible or only insufficiently possible, then one of the goals of EU HTA anchored in the regulation – a reduced effort for the manufacturers in the national benefit assessment dossiers – could not be achieved.

2. Scope and significance of the Joint Clinical Assessment: Participants at the meeting were uncertain about the expected informative value of a JCA. According to the EU regulation, the report should contain a description of the relative effects observed for the endpoints and the confidence intervals, as well as an analysis of the uncertainties and a description of the robustness and limitations of the evidence. Participants questioned whether it will be possible to conduct an assessment in a „value-neutral" way as a purely technical compilation of data. In response, reference was made to previous benefit assessments of orphan drugs by the G-BA: There, too, only the internal and external validity of the data was examined, because the additional benefit was already assumed qua legal fiction. The evaluation of these uncertainties was then reserved for the appraisal process in the individual member states in the context of the EU HTA process, they said.

Some participants were convinced that a large part of the JCA would be based on the „German tradition". The necessity of maintaining the completeness of the required data – as previously in the AMNOG procedure – was emphasised in order to avoid extensive national data demands on the manufacturer. However, it was quite possible that other member states wanted to include surrogate parameters in the procedure that are not considered relevant from a German perspective. Conversely, certain evaluations, which the G-BA has so far demanded from the manufacturers in the AMNOG procedure, would presumably not be fully realisable at the European level, participants explained. As a result, according to the current state of the EU HTA procedure, no EU-wide harmonisation or validation of surrogates was to be expected.

Challenges for the German procedure could arise from the fact that the EU regulation explicitly did not provide for the consideration of evidence generated after approval. As justification, reference was made to the Data Analysis and Real World Interrogation Network (DARWIN) that was launched by the EMA in February 2022. Data from studies beyond RCTs shall be collected and processed there – this should have a positive impact on the future regulatory handling of real-world data. However, paragraph 14 of the EU HTA regulation provides the option of an update of the Joint Clinical Assessment, which would have to be initiated by the Coordination Group.

As a result, a consideration of RWD in the European Benefit Assessment was probably only to be expected in the follow-up to the review process from 2028 onwards, participants explained. The outcome could be that the dossier for the JCA included a more immature data set than the

one used for the JCA. In conclusion, several participants were sceptical that the European procedure would provide a better basis for the subsequent reimbursement amount negotiations

3. Dealing with single-arm studies and evidence from non-RCT studies: The EU HTA Regulation explicitly states in the recitals that „preferably" direct comparative clinical studies that are randomised and blinded should be considered for JCAs. If statements about an additional benefit can be sufficiently obtained via RCTs, then studies based on indirect comparisons „may" also be used, participants outlined. While the EU regulation holds out the prospect of taking into account „specificities of new health technologies", orphan drugs, vaccines and advanced therapy medicinal products are among those mentioned. However, an orphan drug privilege analogous to the German legal situation was not mentioned in the regulation, just as post-market data collections specified in the AMNOG

However, in the methodological guidelines of EUnetHTA21 available so far, single-arm comparisons were assessed sceptically. There, simulated treatment comparisons and matching adjusted indirect comparisons were described as „highly problematic" for methodological reasons. Uncontrolled clinical trials were of „very limited value" for effect estimation, they argued. These assessments were discussed quite controversially by the participants.

While some participants were satisfied that the assessment of single-arm studies in the EU regulation and in the AMNOG procedure was largely characterised by methodological agreement, others were not. The relevant EU documents show a strong focus on classical methods and randomised evidence, and newer methods such as target trial emulation had not yet been discussed by EUnetHTA21.

The aim should be to move from binary classification to a „continuum of evidence", participants noted: The methodology of the European Benefit Assessment should not be „algorithmised", but should rather take the context into account, was the formula. This was also reflected in the approval of new therapies, especially in oncology: in the approval practice of the US FDA, 72% of the newly approved pharmaceuticals in the years 2020 to 2022 were based on non-controlled studies or single-arm studies. At the EMA, this was the case for 53% of approvals in oncology in the same period, it was reported.

In the discussion, the platform participants promoted alternatives for dealing with non-randomised evidence in different nuances. For example, there was a plea that we should be more willing in Germany to deal with observational data. Target trial emulation could be a valid approach and allow for a better handling of confounders. Therefore, however, binding guidelines on design, choice of comparative treatment and data analysis would have to be presented by the G-BA. With these defined protocols, pseudo-populations could be created. The establishment of registries, which would have to be standardised in every disease area, would be the prerequisite. It was pointed out that this process would take years and cost a lot of money: participants were convinced that better real-world data are more expensive than an RCT.

Other discussants advocated a paradigm shift in the use of registries: evidence debates in the context of single-arm studies could be defused if manufacturers started early to enrol patients in registries for certain diseases. In case of doubt, this should apply even if it means disclosing trade secrets, participants said. The prospective design of such studies could circumvent the methodological problems in case of historical controls.

Possible learning experiences from the area of approval for the European benefit assessment procedure: Because

the time limits and procedures would presumably change due to the European benefit assessment and additional time pressure could arise for benefit assessment processes in the member states, participants discussed whether the already existing cooperation between the G-BA and the higher federal authorities BfArM and PEI could be expanded.

It was reported that experts from both authorities were already involved in the consultation in the course of the paragraph 35a procedures. While the G-BA was regularly contacted at a very early stage within the framework of so-called scientific advice at the national level, this early exchange would still have to be established at the European level, participants explained.

Within the framework of a pilot project, national authorities from three EU member states had been brought together at one table since 2022. This could be a blueprint for future European cooperation on tight deadlines, they said. The aim was to answer many of the manufacturers' questions about regulatory processes and benefit assessment at an early stage through simultaneous advice. If the highest possible percentage of relevant data for authorisation and HTA could be determined, this could be a way to allow manufacturers to proceed on a Europe-wide basis.

This approach was generally welcomed by several participants in the discussion. However, the implementation would presumably be hindered by a lack of advisory capacities at the European level. In Germany, there was the „luxurious situation" that manufacturers could consult the G-BA to get advice. In comparison, in the EU HTA, the advisory capacities on the part of the corresponding Coordination Subgroup had not yet been established.

The European benefit assessment against the background of global developments in authorisation and HTA: in the discussion, participants pointed out from a global perspective that the high number of cell and gene therapeutics currently being developed worldwide was encountering a legal framework for benefit assessment in the individual countries that was not yet designed for these challenges. This also applied to the lack of innovative models for reimbursement in national health systems.

Against this global background, it would be a great advantage if the EU member states were able to speak with one voice within the framework of the European benefit assessment. This was because manufacturers set up development plans with the aim of being successful in the USA, it was reported. Therefore, it would be problematic if, in parallel, heterogeneous requirements were formulated from Europe for the studies to be launched.

Other participants disagreed and demanded that there should be no let-up in demanding valid data from manufacturers. EU HTA had the potential to process the evidence in a procedure so that at the end of the process there is an HTA report. This was the added value of the European benefit assessment. In order to achieve this goal, the globally positioned manufacturers could be expected to cooperate with their branches in Europe and the USA.

In conclusion, it was important to turn the challenges of EU HTA into opportunities to strengthen the European pharmaceutical market. More than ten years ago, the AMNOG had triggered a productive discussion. Now the same process was taking place at the European level, with an open outcome to date. Participants recalled that it had also taken years to establish a European approval at that time.

DISCUSSANTS

Dr Jürgen Bausch
Dr Antje Behring
Britta Bickel
Dr Barbara Buchberger
Prof Dr. Heiner Bucher
Prof Dr Dr. Christian Dierks
Claus Burghardt
Dr Jan Daniels-Trautner
Dr Stephan Felder
Dr Mathias Flume
Prof Dr Frank-Ulrich Fricke
Marcel Fritz
Tobias Gemmel
Dr Ulrike Götting
Prof Dr. Wolfgang Greiner
Dr Sandro Gsteiger
Marcus Guardian
Dr Antje Haas
Dr Harald Herholz
Dr Jasmin Hotzky
Pro. Dr Stefan Huster
Dr Florian Jantschak
Dr Elaine Julian
Dr Werner Kulp
PD Dr Stefan Lange
Prof Dr Harald Matthes
Dr Ulf Maywald
Prof Dr. Luca Pani
Dr Hendrik Pugge
Rüdiger Rein
Anja Rettelbach
Dr Heinz Riederer
Prof Dr Jörg Ruof
Dr Jutta Scherer
Henning Stötefalke
Dr Katharina Thiele
Wolfgang van den Bergh
Prof Dr Jürgen Wasem
Dr Sebastian Werner
Stefan Wiefarn
Natalia Wolfram
Prof Dr. Bernhard Wörmann
Bettina Ziegele

ADVISORY BOARD OF THE INTERDISCIPLINARY PLATFORM ON BENEFIT ASSESSMENT

Dr Jürgen Bausch
Britta Bickel
Wolfgang van den Bergh
Prof Dr Wolfgang Greiner
Dr Ulrike Götting
Dr Antje Haas
Dr Harald Herholz
Dr Ulf Maywald
Dr Hendrik Pugge
Dr Heinz Riederer
Prof Dr Jörg Ruof
Prof Dr Bernhard Wörmann

IMPRINT

PUBLISHER
Editorial Advisory Board of the
Interdisciplinary Platform:
Dr Harald Herholz
Kassenärztliche Vereinigung Hessen
Europa-Allee 90
60486 Frankfurt
Germany

PUBLISHING COMPANY
Springer Medizin Verlag GmbH
Am Forsthaus Gravenbruch 5
63263 Neu-Isenburg, Germany
German Commercial Register (HRB):
Berlin Charlottenburg District Court
HRB: 167094 B
VAT-ID: DE 230026696

Telephone: +49 6102 5060
Mail address: info@aerztezeitung.de

EDITORIAL WORK
Dr Florian Staeck
Wolfgang van den Bergh

AUTHORS
Marcus C. Guardian
Dr Antje Behring
Bettina Ziegele
Prof Dr. Luca Pani
Prof Dr Heiner C. Bucher
Prof Dr. Dr. Christian Dierks
Dr Stefan Lange
Dr Sandro Gsteiger
Prof Dr Bernhard Wörmann
Prof Dr Frank-Ulrich Fricke

PICTURE CREDITS
Fotomanufaktur JL / stock.adobe.com

LAYOUT/GRAPHICS
Sandra Bahr
Oliver Hippmann

PRINT
F&W Druck- und Mediencenter GmbH
Holzhauser Feld 2, 83361 Kienberg

Springer Medizin

In cooperation with and with the kind support of AbbVie Deutschland Gmbh & Co. KG, DAK Gesundheit, MSD Sharp & Dohme GmbH, Novo Nordisk Pharma GmbH, Roche Pharma AG, Verband Forschender Arzneimittelhersteller e.V.

INTERDISCIPLINARY PLATFORM ON BENEFIT ASSESSMENT

Impact of EU HTA on the AMNOG procedure

Volume 17
September
2023