European Access Academy

Volume 5, April 2024*

EAA Convention Proceedings

EU HTA – Finding the Right Balance

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Agenda

* The EAA Spring Convention 2024 takes place on April 18/19 at Erasmus University, Rotterdam, The Netherlands

Thursday, April 18th, 2024:

Public Session

15:30 Welcome & Setting the Scene (Maureen Rutten-van Mölken / Jörg Ruof)
15:40 Video Message from DG Santé (Maya Matthews) *
15:45 EU HTA – Finding the Right Balance (Part 1)
- Balancing Involvement of National Experts (Bernhard Wörmann, DGHO)
- Balancing Individual & Societal Need (Antonella Cardone, CPE)
- Balancing Methodology & Uncertainty (Maiwenn AI, ESHPM)
- Balancing Methodology & HTA Categories (Stefan Lange, former IQWiG)

16:45 Coffee Break
17:15 EU HTA – Finding the Right Balance (Part 2)
- Balancing Risk & Benefit (Francesco Pignatti, EMA)
- From ESMO-MCBS & ESMO Guidelines to the patient (Elisabeth de Vries, ESMO)
- Balancing Flexibility & Predictability (Laetitia Mariani, Abbvie)

18:00 Panel Discussion
18:45 End of Public Session
19:30 Dinner Speech:
Defining and Valuing Unmet Medical Need (Marc Van de Casteele, INAMI-RIZIV)

Friday, April 19th, 2024:

EAA Working Session

08:30 Welcome & Setting the Scene (Carin Uyl-de Groot / Elaine Julian)
08:40 Erasmus HTA Research Activities in Scope (Carin Uyl-de Groot)
08:55 GKV-SV Perspective: Status of the EU HTAR (Michael Ermisch, GKV-SV)
09:15 Introduction to Break-Outs (Elaine Julian)
09:30 Break-Out Sessions: Finding the Right Balance Throughout the EU HTA Process
1) Balancing Interaction of EU HTA & EMA
2) Optimizing Expert (patients, clinical experts) Input into JSC & JCA
3) Optimizing the Interface of EU HTA & National Methods and Processes
4) Bias due to Stakeholder Interests

Coffee Break during Break-Out: available from 10:15

11:15 Report from Break-Out Groups & Voting (Facilitators)
12:00 Final Panel Discussion (Maureen Rutten-van Mölken / Mondher Toumi)
12:30 End of Convention

* The video message will be available on *https://www.euaac.org/publications* after the event

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Editorial

EU HTA – Finding the Right Balance

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These are exciting times in which we are witnessing the largest-ever rollout of an HTA process that will affect the market access procedure of medicines and high-risk medical devices of the 27 member states (MS) of the European Union. The legal basis for the joint HTA framework is the European HTA-Regulation, going live on January 12th, 2025. The success of the regulation in terms of accelerating access to real innovations, harmonizing HTA methods, reducing duplication of work, and improving business predictability depends on finding the right balance in several controversial issues. The central theme of the 2024 Spring Convention meeting of the EAA "EU HTA – Finding the right balance" could not be more pertinent and we are delighted to host this meeting at Erasmus University Rotterdam.

Market access of medicines and devices in the EU is known to be a process with a high degree of uncertainty and unpredictability. All stakeholders involved must find the right balance between potential risks and benefits. They navigate a delicate trade-off between type 1 and type 2 errors. In statistical terms, these errors represent the risk of rejecting a beneficial outcome (type 2) and the risk of accepting a harmful outcome (type 1). Considering how this affects the various stakeholders, **developers and investors**, for instance, weigh the risk of investing in drug development with insufficient return on investment against the risk of missing out on profitable opportunities. **Patients** balance the risk of early access to ineffective treatment or treatment with large side-effects with the risk of missing treatment that would have been beneficial. **Health care providers** weigh the risk of overprescribing against the risk of withholding treatment.

National HTA-bodies weigh the risk of reimbursing a drug that is not cost-effective against the risk of denying reimbursement of a cost-effective drug. **Payers** must weigh the risk of additional expenditure on a drug without additional benefit against the risk of not offering the health benefits to their citizens because they controlled costs. And finally, the **European Commission** must balance creating a thorough, efficient EU HTA process without delaying national-level decision-making. What all stakeholders have in common is that minimizing the risk of one error type to occur, increases the risk of the other. It is therefore imperative to find the right balance.

Many aspects of the EU HTA-regulation, that are crucial for finding the right balance between type 1 and type 2 error, continue to be debated. These include the scoping process for defining PICOs (Patient population, Intervention, Comparators, Outcomes), the most efficient way of collaboration between EMA and HTA assessors, the alignment with national HTA processes, and developer and stakeholder involvement. Much will depend on the details in the set of the implementation acts that accompanies the regulation.

As of writing, the first implementation act, on Joint Clinical Assessment (JCA), has just been opened-up for consultation, 10 months before the EU HTA process begins. It particularly alleviates uncertainty on procedural rules and timelines of the JCA and requirements of the developer's dossier. It is good to see that there is somewhat **more time for the scoping process** than expected, since the scoping process will commence concurrently with the developer's submission of the marketing authorization application to EMA rather than 1.5 to 2 months later. Scoping must be finalized within 20 days after the CMPH adopts its list of questions (i.e., 120 days post EMA dossier submission).

The survey to gather MS' PICO needs is replaced by a proposal for the assessment scope from the assessor and co-assessor, on which the MS can give input. This may save the national HTA bodies a lot of time. However, the **unpredictability of the consolidated PICOs** is still a major concern to developers. Once PICOs are consolidated, the Commission requests the developer to submit the dossier, allowing 90 days for submission. The JCA Subgroup will complete the revised draft JCA and summary reports at the latest on the date the Commission grants a marketing authorisation. The HTA Coordination Group should endorse the JCA report no later than 30 days after the Commission grants a marketing authorisation. It will **be challenging to meet all these timelines**.

The first implementation act confirms the expectations that developers will have limited influence on the scoping process. Only when the JCA Subgroup considers it necessary, the developer will be invited to an assessment scope explanation meeting that has to take place within 30 days after the assessment scope is finalised. Additionally, if the JCA Subgroup considers it necessary, they may invite the developer to provide additional information in a meeting or in writing. The developer also has 7 days to point out technical or factual inaccuracies in the revised draft JCA report. Yet, **increased participation from the developer**, who possesses the most comprehensive understanding of the innovation, **does not need to compromise the autonomy of the assessment process**, provided that adequate safeguards are implemented.

The appendix of the first implementation act includes formats and templates for the developer's dossier and the JCA report. Notably, developers must provide information on significant disparities between member states in epidemiology, clinical guidelines, and pathways.

This will likely streamline the assessment of added therapeutic value in national HTA processes, which is crucial given that perceptions of uncertainty and risk depend on context and vary across member states. That is also the reason why the JCA report offers only factual descriptions of endpoint uncertainty. Interpreting and judging this uncertainty falls to the MS. However, there is a **need to develop a more common understanding of acceptable uncertainty levels** among member states. In our opinion, JCA reports should provide a clear assessment of the scientific validity of the evidence to establish a common basis for decision making. This is especially vital for Advanced Therapeutic Medicinal Products (ATMPs) and oncology medicines purporting to cure patients, given that the evidence supporting them at the time of assessment is likely to be underdeveloped, due to the trend of EMA approval relying more on non-randomized, or single-arm studies with intermediate endpoints.

To support decision making under uncertainty, HTA researchers have developed methods like deterministic and probabilistic sensitivity analysis, acceptability curves, scenario analysis, and threshold analysis to systematically identify, analyze, and visualize uncertainty. Similarly, tools like Discrete-Choice-Experiments and Multi-Criteria Decision Analysis have been included in the HTA toolbox to quantify decision trade-offs and support decision-making under uncertainty. Further, tools like Value of Information (VoI) analysis aid in balancing the decision trade-off between delaying for more evidence and accepting the consequences of a decision based on insufficient yet available evidence. Although developed for reimbursement decision-making, the concepts behind these methods

are also applicable to clinical assessments only. Furthermore, these **methods could guide post-marketing study decisions** effectively. This is important as MS will increasingly **have to rely on real-world evidence (RWE)**, especially due to the rise in personalized medicine, rare disease treatments, and potentially curative cell- and gene therapies that require long-term follow-up to gauge full benefits. As a result, decision makers have to deal with growing gaps in evidence, which cannot always be filled with data from randomized studies.

A stronger reliance on real-world evidence is anticipated, yet the EU HTA regulation only addresses post-approval data collection through voluntary collaboration between MS. **Innovative methodologies** have been developed to assess causal effects in the absence of randomization. In the light of the changing nature of the innovations, they **deserve a more prominent place** in the EU HTA regulation.

Hopefully, the EU HTA regulation marks the beginning of a successful joint assessment methodology that gradually incorporates more innovative causal inference methodologies, where necessary, and makes more use of methods for dealing with uncertainty already in our HTA toolbox. A greater consensus on acceptable levels of uncertainty would aid the MS in finding the right balance between type 1 and type 2 errors, thus reducing disparities in access to innovations.

Balancing Involvement of National Experts

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Medicine is a rapidly evolving field. The last three decades have been characterized by innovations in diagnostics and treatment, by increasing complexity and by specialization. Oncology is the prime example, other medical specialties are following. One answer was the introduction of medical guidelines. They provide a bridge between the rapidly increasing, external evidence and the individual patient situation. Guidelines are evidence-based recommendations consented by experts usually under the auspices of medical societies. Within a medical entity, they cover the whole range of health services from prevention, early detection, diagnostic and treatment. They describe the current state of knowledge and provide recommendations.

Guidelines are essential for the definition of unmet medical needs and for the evaluation of innovation. Their definition of the current standard provides the basis for clinical trials comparing new vs old and for the quantification of additional benefit. They are used in the approval of new drugs, new methods as well as in HTA procedures. European guidelines provide a framework. Guidelines on the national level integrate evidence into the local standard of care.

Most importantly, the process of guideline creation has changed and shaped the interaction between experts. The traditional concept of single experts has been widely replaced by networks, as on the national as on the European level. Increasingly these guideline networks also include patients and patient advocates. This has led to the widespread acceptance of guidelines within the health care systems.

Networks provide a higher probability for inclusion of all aspects within a specific medical entity. Networks also provide a higher probability for compensation of inevitable conflicts of interests, apart and beyond the single aspect of commercial issues. On the European level, networks have allowed exchange and inclusion of the different levels of health care balancing differences between national recommendations.

Balancing Individual and Societal Need

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Within healthcare decision-making, determining the value of an individual life against the collective cost/benefit to society poses a complex challenge. Economists and healthcare policy experts have, for many years, used metrics such as the Value of a Statistical Life (VSL) and the Value of a Statistical Life Year (VSLY) to shed light on the economic dimensions of this issue, revealing the scale to which society may be willing to invest in preserving an individual life. As a cancer patient representative organisation, Cancer Patients Europe (CPE) is well aware that, when it comes to healthcare decision-making such as the HTA, a balance must be struck between the needs of the individual and the needs of society. Saving lives as an investment starts with effective preventative measures and increased and accelerated access to treatments.

Strategic healthcare investments can yield significant long-term benefits for both individuals and societies. Moreover, achieving a delicate balance between individual patient needs and broader societal considerations is imperative. With the impending implementation of EU Health Technology Assessment Regulation (HTAR), striking this balance becomes even more crucial, as we have now the opportunity to ensure that the life of a European citizen has the same value no matter where they reside. More collaborative efforts and political will among EU Member States are needed. As we navigate the uncertainties surrounding the practical application of EU HTAR, it is paramount to ensure that both individual patients and societal needs remain at the forefront of healthcare decision-making processes.

Balancing Methodology & Uncertainty

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Increasingly, the EMA sanctions new treatments based on single arm studies, presenting a crucial challenge in quantifying the uncertainty surrounding the treatment effect estimate derived from such studies. To mitigate potential bias in the estimated treatment effect, various measures must be implemented. One such measure involves ensuring that the primary clinical outcome is structured in a manner where without treatment no change in that outcome can be anticipated. Typically, this precludes time-to-event outcomes like progression-free survival and overall survival, as mortality occurs irrespective of treatment. Hence, for oncology drugs, the response rate is often employed when it is considered unlikely that response will occur without treatment.

However, in the context of Health Technology Assessment (HTA), when constructing the Joint Clinical Assessment (JCA), outcomes such as overall survival take precedence, especially in member states (MS) employing the Quality-Adjusted Life Year (QALY) framework for HTA evaluations. Furthermore, an HTA evaluation invariably necessitates a comparator, whether it be an active comparator, best-supportive care, or standard of care. Consequently, external data becomes indispensable to fulfil these requirements, mandating consensus on the appropriate methodology for the selection and matching of external data.

Though this approach may facilitate the estimation of a confidence interval around the measure of relative effectiveness to reflect some of the statistical uncertainty, many uncertainties, e.g. to what extent the study population and the population in the external data are comparable, or the choice between propensity score matching or inverse probability weighting, will not be quantifiable, even with the most advanced methodologies. Consequently, many final JCAs for single arm studies will inevitably translate into significant decision uncertainty for individual MS. Subsequently, each MS must exercise their own discretion, weighing clinical efficacy, costs, and other factors to determine an acceptable threshold of decision uncertainty. Thus, while clear guidance on state-of-the-art methodology may not diminish uncertainty, it does serve to lay bare these uncertainties for the consideration of decision-makers.

Management of Error Potential when Balancing Benefit and Risk

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The balance of benefits and harms is the cornerstone of regulatory decisions for marketing authorisation applications. For "standard" approval, meticulous evaluation of "comprehensive" evidence, adhering to detailed legal requirements regarding submission quality and content, notably from clinical trials, is key. Error control measures in many drug applications focus on the primary efficacy estimate and are based on conventional statistical confidence levels, augmented by corroborative evidence from the submitted dossier.

Expert judgment plays a pivotal role in evaluating the balance between benefits and harms, with the patient perspective being central. International guidelines are in development to ensure robust evidence regarding patient preferences when necessary.

"Conditional" approvals, tailored for situations with high unmet medical needs, entail greater inherent uncertainty. Here, submitted data are less comprehensive, mandating subsequent data submissions to validate decisions. Effective communication regarding uncertainties and risks, coupled with expedited data collection to address and substantiate decisions, is paramount, as underscored by a recent survey involving European regulators.

Uncertainties, limitations in the data submitted, and other concerns may affect the evidence or the value judgments involved in the decision, and require different strategies, based on restricting the marketing authorisation, communication, or collection of further data within an acceptable framework. A focused examination of uncertainties and coping mechanisms pertinent to oncology approvals will be presented.

Despite the extensive evidence requirements, the ability to address all remaining questions robustly and comprehensively is limited. In oncology, for example, many important questions like optimal dose or duration, heterogeneity of response, typically remain after approval albeit addressing these questions often falls outside the scope of the legal requirement for authorisation or post-marketing surveillance. There exists an opportunity for diverse stakeholders, including academia, social insurers, and regulators, to collaborate on establishing a unified framework for optimizing approved treatments. The European Medicines Agency Cancer Medicines Forum has been established to explore the Agency's role in supporting treatment optimization efforts, delineating potential avenues for progress.

Balancing Flexibility & Predictability

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In recent years, disparities in healthcare practices and outcomes have become increasingly evident across European countries. Variability in clinical assessments has been identified as a contributing factor to these disparities, leading to inconsistencies in diagnoses, treatment plans, and patient outcomes. The need for standardized joint clinical assessments has emerged as a critical response to address these challenges and ensure equitable access to high-quality healthcare services across the European Union.

Accelerated patient access to innovation must be our ultimate objective: The EU HTA Regulation is a once in a generation opportunity for meaningful optimization. AbbVie and biopharmaceutical industry partners are highly engaged and committed to collaborating with the EU Commission to ensure an optimal, harmonized pan-European HTA system that supports fast access to patients and meaningful value to member states.

The European Joint Clinical Assessment Implementation Act was enacted on 5th March 2024 within the European Union, represents a significant milestone in standardizing and improving clinical assessments across member states. However, we do realize the need to address several crucial considerations to optimize implementation.

Companies are committed to supporting EU HTA, most are getting prepared through cross functional pilots and adapting internal processes and organization to the new framework.

We do realize a truly European process requires balancing flexibility & predictability –

- With multiple EU HTA PICOs we will need to manage situations without H2H evidence in the future. The new framework needs to adjust the required level of certainty to new situation, allowing alternative sources of evidence and lower threshold for acceptance of indirect evidence. Indirect treatment comparisons should be considered valuable and be able to be conducted despite if disparities in study design and patient populations exist between included studies. The uncertainty caused by potential disparities should be acknowledged and handled in the decision-making processes.
- We are convinced that early involvement of Health Technology Developers (HTDs), patients, clinicians, and other experts throughout the Joint Clinical Assessments (JCA) process increases the predictability and efficiency of the whole assessment process.
- As an example, HTDs contribution in the Scoping Process and their involvement in the process is important for the following reasons:
  - It is the fastest and most efficient way to resolve disputes, provide feedback and respond to questions.
  - It is the fastest and most efficient way to remove roadblocks. For example, if a research question cannot be answered on a timely manner, the HTD could bring for discussion the second-best option.
- Adequate availability of experts for JSCs and JCAs is needed to support more predictable and high quality JCAs
- There is still much uncertainty around the handling of confidential information that will be submitted as part of the JSC and JCA application processes. The current text of the EU HTA Regulation is unclear in this respect. Clarity and guarantees of appropriate handling of confidential information are key, and the lack of such guidance at EU level could lead to backlogs, delays and suboptimal use of the national resources deployed in the context of the HTA Regulation since:
  - Both the industry and the authorities will likely need to engage in time and resource consuming exchanges on the sensitive nature of the data, when third parties (e.g., other pharmaceutical developers) request access to the data submitted under the EU HTA Regulation.
  - Without clear guidance on which data are being protected as commercially sensitive/confidential, applicants may likely be prevented from submitting the highest quality and most detailed information (e.g., unpublished data) which is necessary for a comprehensive and robust assessment.
- The adaptation of national decision-making processes to the new framework enabling the effective use of EU JCAs is crucial to ensure the success of the whole assessment process for all participants.

These recommendations aim to address existing gaps and uncertainties in the regulation, promoting flexibility, predictability, transparency, and efficiency in the joint clinical assessment process across member states of the European Union.

Erasmus HTA Research Activities in Scope

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For more than three decades, Erasmus HTA activities have been at the forefront of HTA research in the Netherlands, Europe, and globally. Our expertise encompasses health economic modeling, cost analysis, and outcomes research, with a commitment to utilizing cost-effectiveness information in healthcare decision-making processes. We have significantly influenced key theoretical and methodological aspects of cost-effectiveness analysis, notably by advocating for the 'societal perspective,' which acknowledges the broader impact of health interventions beyond health outcomes alone. This perspective recognizes the significance of considering benefits and costs beyond health, such as productivity losses and caregiver burden. Our contributions also include the development of pivotal methodologies such as cost-effectiveness acceptability curves, the friction cost-method, methods for assessing caregiver burden, and pioneering valuation studies of instruments like the EQ-5D-5L. Additionally, we have introduced innovative measures such as proportional shortfall and model validation tools, all of which will be leveraged in our ongoing Horizon Europe project, ASCERTAIN.

ASCERTAIN, which stands for Affordability and Sustainability Improvements through New Pricing, Cost-Effectiveness, and Reimbursement Models to Appraise Innovative Health Technologies, aims to enhance current methods of pricing, cost-effectiveness modeling, threshold-setting, reimbursement, and payment. By facilitating a cyclic assessment of broader societal benefits, including costs and risks, ASCERTAIN seeks to promote access to affordable technologies, stimulate innovation and entrepreneurship, and address environmental impacts. Guided by a conceptual framework integrating pricing, health technology assessment, and reimbursement/ payment, ASCERTAIN will develop open-access, user-friendly policy support tools. These tools, including pricing models and value assessment models, will cater to the needs of patients, physicians, payers, regulators, and manufacturers, ultimately enhancing the affordability and accessibility of innovative health technologies across Europe.

In the context of ASCERTAIN's use cases—precision cancer medicine, cell- and gene therapy, and next-generation sequencing (NGS)—uncertainty about outcomes may be significant. This uncertainty, arising from the absence of randomized clinical trials and reliance on short-term, single-arm studies, underscores the importance of carefully assessing the benefit-risk ratio. Both Type I and Type II errors pose risks: inflating or underestimating the perceived benefits of treatments. Striking the right balance between benefits and risks, especially in the absence of a control group, presents a challenge.

While single-arm trials offer valuable insights, they also come with limitations, including weaker evidence strength compared to RCTs and an increased risk of errors. It is imperative for all stakeholders to acknowledge these limitations and carefully interpret the results, weighing the evidence against other available data to make informed decisions about treatment efficacy and safety. Minimizing both types of errors is crucial for accurately evaluating the effectiveness and safety of treatments, ultimately ensuring that patients have access to the most beneficial and safest therapies.

GKV-SV Perspective: Status of the EU HTA R

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The GKV-Spitzenverband (National Association of Statutory Health Insurance Funds) welcomed the consolidation of cooperation between HTA bodies at EU level, when the proposal for the regulation on health technology assessment was initially presented. Joint HTA allows for a better and more comprehensive use of HTA in the decision-making processes of the national healthcare systems, and for strengthening the cooperation already started under the EUnetHTA joint actions.

Even today, I am convinced that the opportunities of the joint HTA by far outweigh the risks. However, the fact that there are only nine months to go until its launch and that many of the questions we have already discussed in previous rounds are still unresolved does give us cause for concern. Furthermore, there is no complete clarity on the timing and methodology - which is not ideal in view of the necessary preparations by all parties involved.

The consultations on the pharma package, including a revision of the authorisation procedure and its deadlines, which began in the middle of the implementation period and which would also directly affect the implementation of the HTA procedure, have certainly not helped to calm things down.

Therefore, we are looking forward all the more to the implementation plan and the publications of the coordination group and the EU Commission in order to be able to make the necessary adjustments to the national procedures as quickly as possible.

At the EAA Spring Convention we will explore more on where we are now and what steps we foresee to take next. I look forward to a fruitful discussion!

Defining & Valuing Unmed Medical Need

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Meeting unmet medical needs is a common objective of many stakeholders in the health system. Nevertheless, there is no unequivocal definition what an unmet medical need is. Especially as to pharmacotherapy, identifying health-related needs must happen in a scientifically valid manner in order to make decisions that are evidence-based.

In 2022 the KCE published for the Belgian Minister of Public Health its report on a method for identifying in a scientific and structural way the most important patient needs that are not being met. This is part of an evolution towards a needs-driven healthcare policy. [1]

The NEED project has started in 2023. NEED stands for *Needs Examination, Evaluation and Dissemination*.

The six Work Packages of NEED have distinct tasks as to concrete realisation of a solid research infrastructure, topics finding and case studies. Several Belgian institutions for public health are involved, as well as stakeholders including researchers, research funders, regulators, patient associations, industry or health care providers. [2]

Finally, a ranking of unmet medical needs[3] disseminated by NEED could be used in reimbursement procedures at the Belgian Health Care Institute, e.g., appraising the scientific evidence in case important patient needs are met.

1) Maertens de Noordhout C et al. KCE Report 348Cs How to identify patient needs? Belgian Health Care Knowledge Centre KCE, Brussels 2021. https://kce.fgov.be/en/publications/all-reports/identifying-patient-needs-methodological-approach-and-application
2) About NEED, financially supported by the Belgian Federal Science Policy through the INFRA-FED-call. https://health-needs.eu/index.php/en/about-en
3) In Dutch https://www.riziv.fgov.be/nl/thema-s/verzorging-kosten-en-terugbetaling/wat-het-ziekenfonds-terugbetaalt/geneesmiddelen/geneesmiddel-terugbetalen/onbeantwoorde-medische-behoeften-unmet-medical-need ; in French https://www.inami.fgov.be/fr/themes/soins-de-sante-cout-et-remboursement/les-prestations-de-sante-que-vous-rembourse-votre-mutualite/medicaments/remboursement-d-un-medicament/besoin-medical-non-rencontre-unmet-medical-need

EAA Research Survey

Interim Results

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In preparation for the European Access Academy's (EAA) Spring Convention 2024 'EU HTA – Finding the Right Balance' a research survey was developed by the EAA Faculty to generate multi-stakeholder input in key areas related to the European (EU) Regulation 2021/2282 on Health Technology Assessment (EU HTAR; 1):

i. the interaction of EU HTA & the European Medicines Agency (EMA),
ii. optimizing expert input into joint scientific consultations (JSC) & joint clinical assessments (JCA),
iii. optimizing the interface of EU HTA and National HTA methods and processes,
iv. on bias due to stakeholder interests, and
v. on the assessment of uncertainty in evidence for EU HTA.

The survey was shared with a wide audience via digital channels including the EAA website, emailing to the EAA network, and posts on professional social media and the EU Health Policy Network. Responses were collected on a 4-point Likert Scale ranging from "yes", via "rather yes" and "rather no" to "no", or via ranking of response items by priority and were supplemented with free-text qualitative responses. Hereafter, we present interim results of the first n=36 response submissions (n=36) to the survey with respect to the quantitative questions (expert input, interface EU HTA & Natlional HTA, bias) and one of the ranking questions (uncertainty). The data cut for final analysis is planned for April 20th, after completion of the EAA Spring Convention, with a projected total number of 50-60 responses.

Respondents cover eight European countries (Belgium, France, Germany, Italy, the Netherlands, Poland, Spain, Switzerland) and one respondent represents India. In addition, several respondents identify as representing roles spanning global (n=4) or EU-wide (n=9) responsibilities. All previously identified key stakeholders and collaborators in the joint EU HTA process (2) are represented in the sample.

According to the submitted responses, **experts** (defined as patients and clinical experts) are not **sufficiently included or being heard** in the upcoming JSC / JCA processes. 61 % responded "no" or "rather no", while 39 % responded "rather yes" or "yes" (Figure 1a).

Furthermore, 64 % of respondents consider the principles of 'transparency' and 'competency' being balanced in the **EU HTA position on Conflict of Interest (CoI),** while 36 % consider them not being balanced ("rather yes" or "yes" vs. "no" or "rather no"; Figure 1b).

When asked to evaluate **how the establishment of EU HTA will affect national appraisal decision making**, the majority responded positively that the latter will be facilitated (56 % "rather yes" or "yes" vs. 44 % "no" or "rather no") but only 39 % responded that it will be accelerated (39 % "rather yes" or "yes" vs. 61 % "no" or "rather no"; Figure 1c).

Notably, three quarters of respondents indicate that EU HTA is not sufficiently prepared to face expected **uncertainty in evidence** to be provided in the EU HTA submission for the JCA (75 % "no" or "rather no" vs. 25 % "rather yes" or "yes"; Figure 2a).

Further, respondents were asked to rank suitable approaches to address residual questions and remaining uncertainty regarding evidence in order to increase confidence in decision making. All suggested options were ranked similarly with relative cumulative weight points (compared to the maximum possible points) ranging from 64 % (Integration of the patient perspective into the assessment) to 77 % (Integration of the clinical perspective into the assessment; Figure 2b).

With less than one year remaining until the stepwise application of the EU HTAR, starting with oncology medicines and ATMPs, it will be crucial to 'find the right balance' in a range of critical topics to achieve the aim of the regulation, i.e., improving patient access to life-saving innovative health technologies (1). The importance of involving experts at various stages of the EU HTA process to balance a "technical" and data-driven assessment with the clinical context and relevance of outcomes for patients, has been described at length (2-7). Still, the majority of the multi-stakeholder respondents to this survey feel that the clinical and patient voices are not sufficiently included in JSC and JCA, as currently defined. EU HTA principles for managing conflict of interest, which is a crucial challenge with the risk of excluding relevant expertise from the process, appear to be balanced in the view of the majority of respondents (3-4,8). The recently published draft of the European Commission's Implementing Regulation on JCA details patient and clinical expert involvement in JCA however, further challenges remain to translate this regulation into meaningful input for the joint HTA work (3-4,9).

The joint clinical assessment report generated in EU HTA procedures will be provided to the Member States for consideration in their national decision making (1). However, many challenges regarding the interface of EU HTA and national processes have been identified, including capacity, timelines and required adaptation of national legal frameworks (10-13). This is reflected in the survey responses, where the majority do believe that EU HTA will facilitate national appraisal decision making but only a minority also believe that they will be accelerated. Considering the regulation's aim to improve patient access to innovative health technologies it will be critical to identify specific details and aspects of these challenges in order to overcome the main obstacles preventing this goal from being achieved.

With the shift in treatment paradigms and increasingly targeted treatments, uncertainty in evidence will play a relevant role and is expected to generate discussions in future assessments, in particular for oncology and ATMPs (14-18). However, only a quarter of respondents believe that EU HTA is sufficiently prepared to face this challenge. Approaches like increased involvement of experts, including patients, clinicians and also the health technology developers, as well as a balanced approach to accepting both, established and innovative methods for comparative assessments, should be considered.

The findings summarized above are initial perspectives derived from the interim analysis of the EAA research survey and will form the basis for in-depth discussions during the EAA Spring Convention 2024 at Erasmus University in Rotterdam. The outcomes of these discussions, together with the final survey responses including all qualitative input, will be analysed in detail for comprehensive discussions and conclusions on i) the interaction of EU HTA & EMA, ii) optimizing expert input into JSC & JCA, iii) optimizing the interface of EU HTA and National HTA methods and processes, iv) bias due to stakeholder interests and v) the assessment of uncertainty in evidence for EU HTA.

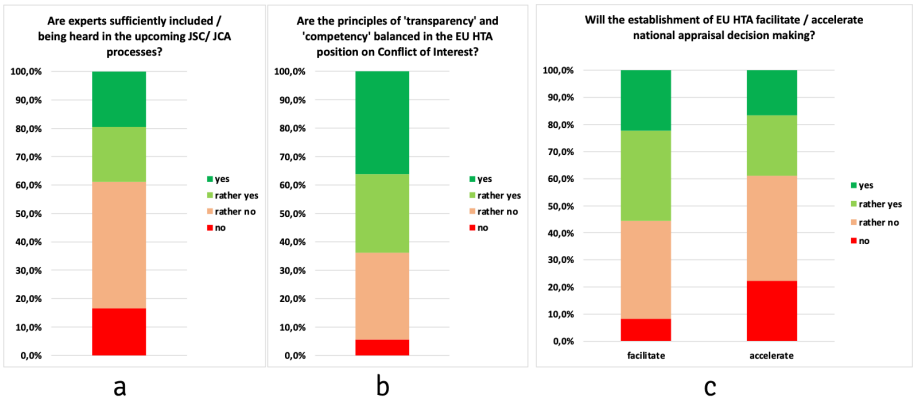

Figure 1a-c: Percentage of respondents (of a total of n=36) who responded "yes", "rather yes", "rather no" or "no" to the respective questions on expert involvement in EU HTA (a), the EU HTA position on CoI (b) and the interface of EU HTA and national decision making (c).

EU: European Union, HTA: health technology assessment, CoI: conflict of interest, JSC: joint scientific consultation, JCA: joint clinical assessment

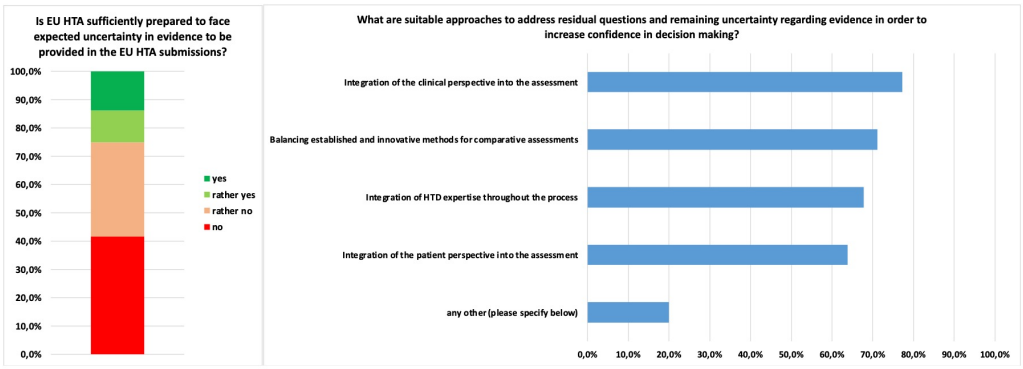

Figure 2: Percentage of respondents (of a total of n=36) who responded "yes", "rather yes", "rather no" or "no" to the question on preparedness of EU HTA to face uncertainty in evidence (a) and ranking of approaches to address residual questions and uncertainty regarding evidence based on cumulative weighting relative to the maximum possible weight (b).

EU: European Union, HTA: health technology assessment, HTD: health technology developer

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Outlook EAA Fall Convention 2024 in Rome, Italy

Transitioning from Preparation to Implementation: *Critical Points & Learnings*

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In 2014 the British Neurosurgeon Henry Marsh published his famous Stories of Life, Death and Brain Surgery titled: 'Do No Harm'. In the preface he admits that the life of a brain surgeon is never boring and can even be profoundly rewarding, but this comes at a price: 'You will inevitably make mistakes and you must learn to live with the occasionally awful consequences. You must learn to be objective about what you see, and not lose your humanity in the process'. Thorough preparation, as Henry Marsh repeatedly points out, is key for any successful surgery.

What applies to the individual brain surgeon's efforts also applies to a whole health care system. 'Doing no harm' and aiming for 'best outcomes for patients and society as a whole' is the ultimate aim of the EU HTA Regulation (EU HTA R). In January 2025 it will transition from preparation to implementation – ideal timing for EAA's 2024 Fall Convention in Rome to share experience and learnings gathered during this transition phase and discuss the level of preparedness of the various stakeholders.

Setting up the Coordination Group, the respective subgroups, the HTA Stakeholder Network, and the IT Platform were key activities achieved during the preparatory phase on the side of the European Commission (EC) and the Member States. In addition, based on a Service Contract with the EC, the EUnetHTA 21 consortium developed a variety of guidance documents. However, the development and publication of implementing acts by the EC and detailed guidance documents by the Coordination Group, as set out in the regulation, are delayed.

This is resulting in considerable burden on Health Technology Developers (HTDs) who require clarity on details of the requirements to be able to develop their EU HTA Dossiers for the products falling under the initial application of the EU HTA R – i.e., oncology and ATMPs. Delay of implementing acts and guidance documents, however, is not the only 'roadblock' to overcome; lack of resources and capacities in the Coordination Group, in the Member States, and within DG Santé, as well as limited opportunities for Joint Scientific Consultations (JSCs) are further areas of concern during this transition phase to the implementation of the EU HTA R.

Beyond those procedural challenges, ultimately, the success of the Regulation will depend on the establishment of an inclusive societal dialogue alongside the evolving JSC and JCA procedures. Sharing experience on the pain points and learnings across all participating stakeholders and collaborators is therefore on the agenda of the EAA Fall Convention 2024. The focus will be on Oncology and ATMP Medicines, as they will be first within the JCA process.

Considering Italy's current efforts to modernize AIFA and to thus optimize national procedures for health innovation and patient access, Rome appears to be an ideal venue for the upcoming EAA Convention. This proactive and preparatory action by the Italian government is an essential step forward and underlines the importance of linking the EU JSC & JCA with the national HTA bodies and their procedures in order to turn the Regulation into a success for both, the Members States and the Union.

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Contributors & Imprint

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Imprint

Publisher:
The European Access Academy
The EAA secretariat is hosted by r-connect.
r-connect GmbH
Hauensteinstr. 132, 4059 Basel, Switzerland
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Publication Series:
EAA Convention Proceedings Volume 5, 2024
ISSN: 2813-3390 (Print) & 2813-9438 (Online)

Editorial Work:
Jörg Ruof & Elaine Julian

Images/ Copyrights:
Title Image: Curtesy of Erasmus University, Rotterdam, The Netherlands

Print:
Uehlin Druck- und Medienhaus, Hohe-Flum-Str. 40, 79650 Schopfheim, Germany
www.uehlin.de

The EAA is an initiative hosted by Copenhagen University, Utrecht University, Vlerick Business School, Agència de Qualitat I Avaluació Sanitàries de Catalunya, Erasmus University and endorsed & funded by: Springer Healthcare, Abbvie, AstraZeneca, Bayer, Novartis, Pfizer, Roche, Sanofi, vfa, leem and efpia.

EAA Publication

Desmet T., Julian E., Van Dyck W., Huys I., Simoens S., Giuliani R., Toumi M., Dierks C., Dierks J., Cardone A., Houÿez F., Pavlovic M., Berntgen M., Mol P., Schiel A., Goettsch W., Gianfrate F., Capri S., Ryan J., Ducournau P., Solà-Morales O., Ruof J.: An inclusive civil society dialogue for a successful implementation of the EU HTA Regulation: Call to action to ensure appropriate involvement of stakeholders and collaborators. JMAHP ***12****(1), 21-34 (2024).*
doi: https://doi.org//10.3390/jmahp12010004

European Access Academy

The EAA is a multi-stakeholder initiative aiming to facilitate and support the development of a joint European value framework for the assessment of innovative health technologies.

ISSN 2813-3390 (Print)
ISSN 2813-9437 (Online)

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