European Access Academy

Volume 4, October 2023*

EAA Convention Proceedings

Haemato- / Oncology – A Pace Maker for EU HTA

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Agenda

Wednesday, October 18th, 2023:
Public Session

15:30 Welcome (Oriol Solà-Morales/ Jörg Ruof)

15:45 Setting the Scene:

- The Haemato-Oncology Pipeline – EMA Overview (Caroline Pothet, EMA)
- Pace Making for EU HTA – Coordination Group Perspective (Roisin Adams, HTA CG)
- What is ESMO doing to support EU HTA? (Elisabeth de Vries, ESMO)
- EHA Perspective on EU HTA (Martin Kaiser, EHA)
- Oncology HTA – National Insights from Germany (Bernhard Wörmann, DGHO)
- Industry Perspective (Brian Cuffel, Bayer Pharmaceuticals)

17:15 Coffee Break

17:30 Panel Discussion

19:00 End of Public Session

Thursday, October 19th, 2023:
Working Group Session

08:30 Welcome (Oriol Solà-Morales/ Jörg Ruof)

08:35 Early Bird Talk: HTA in EU – Quo Vadis? (Eleni Pitta)

09:00 Introduction to Break-Out Sessions

09:30 Break-Out Sessions: Pace Maker for EU HTA

- Medical Societies' Role in EU HTA
- Role of Clinical Guidelines in EU HTA
- Interface of MCBS & HTA
- Defining 'Best-Available Evidence' for EU HTA

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

11:15 Report from Break-Out Groups & Voting

12:00 Final Panel Discussion (Moderators: Marcus Guardian, IHSI & Oriol Solà-Morales)

12:30 End of Convention

*The EAA Fall convention 2023 is taking place on October 18/19 at
Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS), Barcelona, Spain

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Editorial

Haemato-/Oncology – A Pace Maker for EU HTA

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In 2022, the European Medicines Agency (EMA) issued 89 positive opinions with 29 thereof (33%) covering Haemato-/Oncology conditions[1]. Furthermore, 5 out of the 6 Advanced Therapy Medicinal Products (ATMPs) that received a positive opinion in 2022 were covering Haemato-/Oncology conditions. Those numbers far surpass those of any other disease area. Rightfully, Haemato-/Oncology may therefore claim to be a Pace Maker for innovative research in medicine paving the way for advanced, molecular, targeted treatments in an ever more diverse and individualized therapeutic environment. Reflecting this trend, article 7 of the EU HTA regulation[2] determines that cancer medicines and ATMPs will be in scope of the initial phase of EU HTA Assessment from January 2025 – December 2027, further confirming Haemato-/Oncology as a Pace Maker also for EU HTA.

From the perspective of the Spanish Representative within the EU HTA CG and from the perspective of Fundació HITT we very much welcome the EAA Fall Convention in Barcelona as well as the subsequent ESMO meeting taking place in Madrid. Advancing Haemato-/ Oncology care as well as respective HTA assessments is a key public health priority in Spain.

At the Fall Convention 2023 the EAA is once again specifically addressing Haemato-/Oncology conditions. While the inaugural convention in May 2022 in Copenhagen examined the connection between two key cancer-related initiatives of the European Commission, the 'EU HTA regulation' and 'Europe's Beating Cancer Plan'[3], the focus of the Fall Convention 2023, hosted by the AQuAS Institute (Agency for Health Quality and Assessment of Catalonia) in Barcelona is on the evolving role of the scientific societies and their key deliverables such as clinical guidelines etc. within the EU HTA process. Therefore, three clinical experts are covering the perspective of the European Society for Medical Oncology (ESMO; E. de Vries), the European Hematology Association (EHA; M. Kaiser) and a key national society, the German Society for Haematology and Medical Oncology (DGHO; B. Wörmann) on the EU HTA regulation in their respective impulse presentations. Prior to these clinical insights an introductory overview of the Haemato-/Oncology pipeline is provided by C. Pothet from EMA and R. Adams, Head of the EU HTA Coordination Group (CG), is sharing the CG's considerations regarding those innovative medicines. The impulse presentations at the Public Session conclude with the Spanish Health Policy position and a reflection from an industry point of view before the floor is opened for questions from the audience in a panel discussion.

Building on the insights from the public session, the convention resumes with the EAA Working Session including a series of break-out sessions. Data of an interim-analysis derived from the related pre-convention survey are presented in this volume # 4 of the EAA Proceedings and will inform the discussions in the respective breakout sessions on i) Medical Societies' Role in EU HTA, ii) the Role of Clinical Guidelines in EU HTA, iii) the Interface of ESMO's Magnitude of Clinical Benefit Scale (MCBS) and EU HTA, and iv) on the Definition of Best-Available Evidence for EU HTA.

At this time of the preparation phase, it is important that all stakeholders, as representatives of clinical societies or member states, get prepared for the changes that will happen soon and participate in the debates to make their voices heard and shape the future of innovation in the EU.

We wish all participants a great and insightful EAA Convention and – hope you will enjoy reading this EAA Proceedings Volume # 4.

Best regards
Eleni Pitta & Oriol Solá-Morales

1 European Medicines Agency. Human Medicines Highlights 2022. https://www.ema.europa.eu/en/documents/report/human-medicines-highlights-2022_en.pdf (accessed Aug 17th, 2023)

2 The European Parliament and the Council of the European Union. 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. Official Journal of the European Union L 458/1. 2021 Dec 22; https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32021R2282 (accessed Aug 17th, 2023)

3 European Access Academy. EAA Convention Proceedings. Volume 1, August 2022. Europe's Evolving HTA Regulation and Its Relevance for Beating Cancer. https://irp.cdn-website.com/e52b6f19/files/uploaded/Abstract%20Booklet%20EAA%2005%202022.pdf (accessed Aug 17th, 2023)

The Haemato-Oncology Pipeline – EMA Overview

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For many years already, oncology has been the therapeutic area with most approvals, reflecting the dedication of many developers in this area. Last year, the Committee for Human Medicines (CHMP) recommended 89 medicines for marketing authorization; amongst those, 23 were in oncology. Nevertheless the need for new medicines against cancer remain high; In 2020, 2.7 million people in the European Union were diagnosed with cancer, and another 1.3 million people lost their lives to it, including over 2,000 young people; according to recent figures, cancer cases are set to increase by 24% by 2035, making it the leading cause of death in the EU1. It is therefore critical that we all work together to improve patient access to innovative, potentially life-saving therapies.

At the Agency, we are highly committed to contribute to this fight against cancer and ultimately help patients to access treatments faster by

- supporting the integration of scientific and technological progress in the development of medicines (e.g., precision medicine, biomarkers, 'omics and ATMPs) and ultimately into patient treatment;
- using oncology products as a pathfinder, increasing the sustainability and availability of expertise in the European Network by ensuring a good understanding of future challenges derived from innovative medicines via horizon scanning and interactions with stakeholders involved in the lifecycle of medicines development, and by
- fostering collaborative evidence generation, enhanced interactions and increased understanding of positions on data requirements from all relevant stakeholders, including HTA and pricing and reimbursement authorities.

At the EAA Fall convention, you will hear about some of the above initiatives together with an overview of the recent and future trends in the haemato-oncology pipeline.

Pace Making for EU HTA – Status Update and Needs from a Coordination Group's Perspective

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The EU Regulation on Health Technology Assessment (EU) 2021/2282 entered into force in January 2022. It sets up a legal framework for strengthened EU cooperation on health technology assessment (HTA). The aim is to improve access for EU patients to innovative technologies in the area of health such as medicines and medical devices. The HTA regulation also aims to reduce the duplication of efforts for national HTA authorities and industry and to increase business predictability and the long-term sustainability of EU HTA cooperation.

The Member State led HTA Coordination Group is established along with four subgroups and as we move towards 2024 the implementation phase is well underway. The architecture of the future system is being built including development of the necessary Implementing Acts, IT infrastructure, a Stakeholder Network and an EC Secretariat.

This EU HTA system emerges from a rich history of HTA collaboration across EU countries which intensified during the work of EUnetHTA21. The adoption of clear and robust methodological guidelines to underpin the joint work will be crucial and is one of the main priorities for the HTACG and its subgroups. Sufficient and sustained resourcing of the EU HTA System will be essential for a strong and efficient process that will allow the aims of the Regulation to be realised.

Progress to date as well as future planning will be outlined as well as the core elements of the work in development.

What is ESMO doing to support EU HTA?

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The European Society for Medical Oncology (ESMO) works to ensure access to, and the availability of, medicines so that patients with cancer receive the best possible treatment available and is also developing tools and resources that can support countries to assist in HTA processes and in achieving sustainable cancer care. This includes:

1. ESMO-MCBS: The ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) was developed to assess the value of cancer care, prioritize medicines and address the challenges of the appropriate use of limited resources to deliver cost-effective and affordable cancer care. When used from the outset of Joint Clinical Assessments, the ESMO-MCBS may be instrumental in prioritizing medicines and helping to avoid duplication of efforts. It is used as part of HTA processes by authorities, regions, and oncology societies in various countries. The ESMO-MCBS v1.1 for solid tumors will soon be upgraded to v 2.0. Moreover, the ESMO-MCBS:H for hematological malignancies has been recently released.

2. ESCAT: The ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) contributes to the rapidly evolving field of precision medicine. This scale aims to facilitate the identification of those patients with cancer who are likely to respond to precision medicines and help make treatment more cost-effective. It also defines clinical evidence-based criteria to prioritize genomic alterations as markers to select patients for targeted therapies. This scale may be a helpful tool to inform on the value of new medicines, the priority setting, and coverage decisions.

3. Approach to identify bias in studies: ESMO has described a structured approach to identify bias that may distort the results of clinical studies. This approach may help with enhancing nuance in HTA evaluation processes.

4. Value-based reimbursement model: ESMO, with the London School of Economics, is developing a geographically adapted value-based reimbursement model to tackle issues related to the reimbursement of expensive, innovative cancer medicines. When completed, it may be of great value for supporting reimbursement decisions made at the national level.

5. ESMO Clinical Practice Guidelines: The ESMO Clinical Practice Guidelines are prepared and reviewed by experts and based on the findings of evidence-based medicine. They provide medical oncologists with a set of recommendations to provide patients with the best care options.

6. ESMO surveys: ESMO studies and monitors the availability, out-of-pocket costs, and accessibility of cancer medicines and technologies in Europe and globally. Work is ongoing on version 2.0 of the Antineoplastic Medicines Study (ANMS). ESMO has also conducted a study on the Availability and Accessibility of Biomolecular Technologies in Oncology in Europe to provide a comprehensive overview of the availability of biomolecular technologies to patients, the status of their use and prescription, barriers to access, and potential economic issues related to cost and reimbursement.

Finally: ESMO stands ready to help the EU institutions, HTA bodies, and the wider healthcare professional community implement the HTA Regulation through the support of its dedicated tools and members' expertise.

EHA Perspective on EU HTA

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Haemato-oncology continues to be at the forefront of innovation in cancer therapeutics. European haemato-oncologists and patients in particular have played an integral part in evidence generation for global regulatory approval of many novel therapeutic technologies over the past decade – a success that has not always been matched by patient access to the same technologies.

The advent of the EU HTA process creates novel incentives and opportunities for including clinically relevant value assessments from early stages of development, which could potentially facilitate access to truly innovative therapies in the future. In addition, with a growing number of off patent medicines in haemato-oncology, re-investigation and re-examination of biologicals under HTA criteria could offer opportunities for improved use of innovative medicines in European healthcare systems.

Inevitably, these processes will require relevant clinical expertise to evaluate and identify true innovation, patient-centricity of trial designs, as well as relevance and deliverability in a European healthcare system context. Involving clinical experts and researchers in strategic partnerships, ranging from horizon scanning to considerations around feasible clinical trial design and practical delivery of treatments and diagnostics, seems essential for successful long-term implementation of EU HTA, especially in a highly specialised and rapidly changing field like haemato-oncology. However, potential barriers for experts to get involved need to be considered, and new initiatives are likely required for the next generation of haemato-oncologists to perceive active involvement in HTA processes as a sustainable career opportunity.

Oncology HTA – National Insights from Germany

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Health technology assessment (HTA) of new drugs is one element in the evaluation of novel medical strategies. In Germany, this regulatory process was only established in 2011 with the so-called AMNOG process. Since then, assessment of oncological drugs has accounted for almost 50% of all procedures. This has led (forced) the respective medical societies such as the DGHO German Society for Hematology and Oncology to build up internal but also external structures in order to efficiently cooperate in this process. Central elements are:

Organization: In Germany, more than 180 medical societies are organized within the AWMF Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften. Within this organization a committee of 25 medical societies with focus on drug therapy was formed, under the leadership of the DGHO. Thus far, the committee has issued 6 reports on AMNOG results. Amongst others, they address open questions such as the methods for assessment of quality of life or discrepancies in the assessment of drugs for acute and chronic diseases.

Experts: The involvement of medical societies has led to a substantial change in the recruitment of experts. The former procedure of appointment of single persons has been largely substituted by groups of experts. Those groups comprise 5 to 15 experts nominated by the respective medical societies. Criteria are personal expertise and involvement in guidelines but also diversity with regard to sex, age and workplace. These experts write the statements and participate in the hearings by the G-BA.

Standard of Care: The increasing involvement and impact of medical societies in the HTA process has led to legal fine tuning of the AMNOG process in 2019. Now, medical societies are involved in the early process of consultation from pharmaceutical companies. The expert networks provide a summary focusing on the current standard of treatment, diagnostic procedures, relevant subgroups and endpoints (PICO). In 2022, 243 statements were provided.

In Germany, the cooperation between HTA and medical societies has developed into a win-win-situation. The HTA process benefits from access to expert networks and independent guidelines, experts and medical societies benefit from profound insight into the dossiers on new drugs.

Industry Perspective

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Implementation of EU-HTA regulation represents an important opportunity for cancer patients in all EU countries who seek to benefit from earlier access to new oncology treatments resulting from more timely and harmonized/consolidated HTA assessments of the clinical evidence. The regulation applies to new oncology and advanced medicinal therapeutic products starting in 2025, concurrent with exponential growth of new cancer trials for rare tumors and hematologic cancers.

Advances in genomic science and new modalities of treatment are driving changes in regulatory standards and scientific and drug development approaches for which HTA must keep pace. Several trends in oncology are already predictable such as acceleration of novel modalities into early line treatments (e.g., FDA project Frontrunner), novel endpoints that reflect cure, long-term benefit, and/or meaningful change in disease, and continued disease fragmentation into subgroups defined by pan tumor oncogenes. Although these approaches will bring substantial benefits to patients, they are not unique to oncology and some common measures are needed to avoid bottle necks in patient access to the most innovative treatments entering the EU.

- Guidance that addresses challenges regarding the ability (or inability) to conduct RCTs, intermediate and novel endpoints, comparators, magnitude of clinical benefit, and the regulatory context which may lead to conditional marketing authorization.
- Ensure that the first JCAs do not disqualify certain types of evidence or methods that are otherwise accepted medical and scientific standards within oncology while also adequately characterizing residual uncertainty in the evidence.
- Real-time evaluation of the first JCAs and ensure that they evolve over time reflecting standards for oncology development, regulatory approval, and academic developments in scientific areas including clinical and HTA methods.

In the long-term, a centralized HTA process can more effectively keep pace with fast moving therapeutic areas such as oncology. However, with only a year remaining until implementation, pragmatic solutions focused on the most critical challenges at both the EU and member state levels will be required to ensure that the clinical assessment of new cancer therapies reflect the benefits to patients according to accepted medical and scientific standards in oncology.

Clinical Trials in Oncology: Lessons to be learned

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The increasing number of approvals for innovative therapies in the Oncology area represents a milestone of clinical research which allowed to change, in a way or another, the course of a number of oncological diseases. Nevertheless, the positive perspective of finding more and more effective treatments for cancer is counterbalanced by several possible biases generated during a perhaps too fast assessment of novel treatments. For example, with the rationale to supply a valid treatment in those areas characterized by a very high (if not absolute) unmet need, the accelerated approval procedures represent a tool which rapidly offers more options to patients, but, on the other hand, is often affected by a limited vision of a hidden profile of the drug itself as the data are not definitive. This is due to the acceptance by payers of quite weak endpoints, of improper phase I or II trial designs, as well as other biases that may occur in the complex of data filed by producers for approval. As a mere example, the novel chapter open recently in Oncology by immune checkpoint inhibitors, brought about a number of too eager interpretations of weak clinical outcome data with the purpose of guaranteeing an early access to a given product to patients lacking alternative options. The early approval procedures, however, demonstrated to be a double-sided coin: on one side allowing the almost immediate access to the market, on the other side, in the majority of cases, failing to provide the expected benefits in terms of incremental clinical improvement. Moreover, enrollment of patients in a certain trial profile, will also subtract the same patients to more properly structured clinical trials, potentially able to produce broader certainty about efficacy and safety outcomes. This, in turn, would be likely translated in a lesser number of treatments available, but, on the other hand, it would allow significantly reduced chances of useless or even dangerous outcomes. As a proof, examples of post-marketing withdrawal of drugs claimed as innovative are not sporadic, but rather represent a not negligible percent of approvals. Another aspect which, as a matter of fact, appears neglected during accelerated approval procedures in Oncology is the correct definition of the dose range to be used in a given condition. It is not rare that dose studies conducted in a short-term span, with minimal design trials, result in a therapeutic failure, either for lack of efficacy, or for the occurrence of unmanageable safety issues. In parallel, this would lead to unravel that doses which are actually effective are indeed far lower than the ones investigated within the trial. In conclusion, all the above observations should represent a substantial rationale for a deeper reflection whether or not it is more convenient for the sake of either patients, payers and producers, to be more cautious in pushing data from accelerated access trials; or, instead, to focus more resources on long-term trials which promise to generate more reliable and appliable data. Time is a gentleman who always pays well.

With the contribution of: Carlo Maria Bellanca MD; Mattia De Riggi MD; Egle Augello BSc.

EAA Research Survey

Interim Results

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In preparation for the EAA Fall Convention 2023 'Haemato- / Oncology – A Pace Maker for EU HTA' a research survey was developed by the EAA Faculty to generate multi-stakeholder input on the role of clinical professional associations, European clinical guidelines, the ESMO-MCBS and the concept of 'best-available evidence' in 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" and were supplemented with free-text qualitative responses. Hereafter, we present interim results of the first n=46 response submissions to the survey with respect to the quantitative questions. The data cut for final analysis will be October 20th, after completion of the EAA Fall Convention, with a projected total number of 60-70 responses.

Respondents cover 11 European countries (Belgium, Croatia, France, Germany, Greece, Italy, the Netherlands, Portugal, Spain, Switzerland, United Kingdom). In addition, several respondents identify as representing roles spanning global (n=10) or EU-wide (n=9) responsibilities. All previously identified key stakeholders and collaborators in the joint EU HTA Process[2], apart from policy makers, are represented in this interim analysis.

According to the submitted responses, the **role of Clinical Professional Associations** such as the European Society for Medical Oncology (ESMO) in EU HTA varies depending on the aspect of the process. Of the respondents, 52% (including the answers "yes" or "rather yes") believe that clinical associations should be involved in co-shaping the HTA methodology. The vast majority believe that clinical associations should be involved in co-shaping the scoping (PICO) schemes (83%), identifying appropriate individual experts to develop and represent the association's point of view (96%), and collaborating across national and EU level associations to support the Member States with expert advice for each individual HTA assessment (87%) (Figure 1).

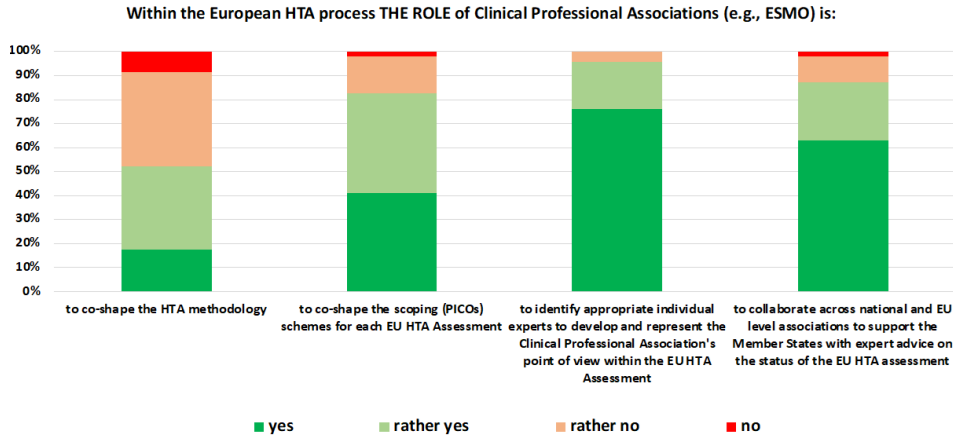

Figure 1: Percentage of respondents (of a total of n=46) who responded "yes", "rather yes", "rather no" or "no" to the questions regarding specific aspects of the role of clinical professional associations in the EU HTA assessment process.

When asked to evaluate **European Clinical Guidelines** regarding their applicability for EU HTA procedures, responses are similar across the different aspects (Figure 2). 59% of respondents (including answers "yes" or "rather yes") consider guidelines 'fit for purpose' to shape the Member States' responses to PICO surveys, 57% consider them 'fit for purpose' for JCAs, 52% consider them well aligned with the national guidelines in the various EU Member States, 54% consider them 'up to date', i.e., designed as living guidelines, and 70% believe that they sufficiently take into account the relevance of safety considerations within the EU HTA assessment (Figure 2).

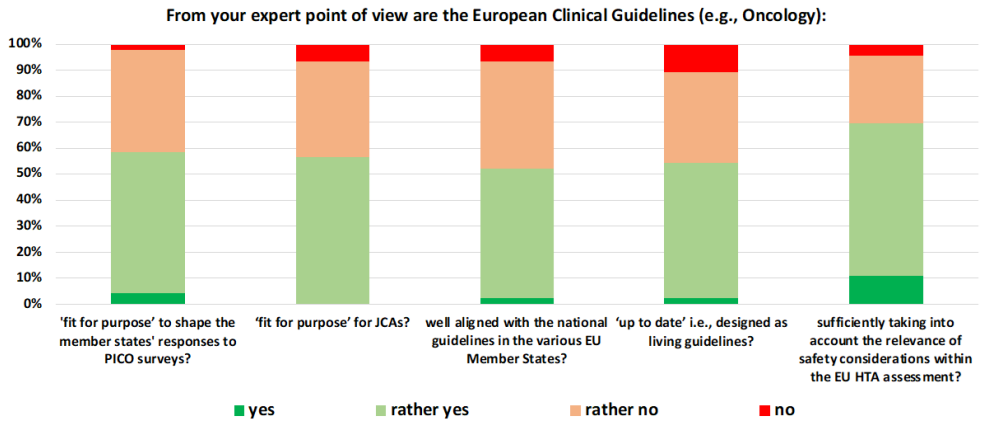

Figure 2: Percentage of respondents (of a total of n=46) who responded "yes", "rather yes", "rather no" or "no" to the questions regarding specific aspects of the applicability of European clinical guidelines for EU HTA procedures.

The **ESMO Magnitude of Clinical Benefit Scale** (ESMO-MCBS) is a tool to assess the magnitude of clinical benefit of new cancer therapies[3]. The respondents who were aware of this tool were asked about the suitability of the ESMO-MCBS for (EU) HTA. Of them, 33% (including answers "yes" or "rather yes") believe that the ESMO-MCBS is currently informing national appraisal procedures, and that the scale is 'fit for purpose' for EU HTA. 23% view the ESMO-MCBS as being aligned with the EU HTA assessment regarding underlying methodological criteria, 25% view it as sufficiently addressing the challenges of the EU HTA scoping (PICO) process, and 41% perceive it as being sufficiently 'up to date' to inform the EU HTA Joint Clinical Assessments. On the other hand, 80% feel that the ESMO-MCBS is effectively addressing ESMO's perspective on the relevance of clinical trial endpoints in relation to patients, clinical practice, and health policy decision making (Figure 3).

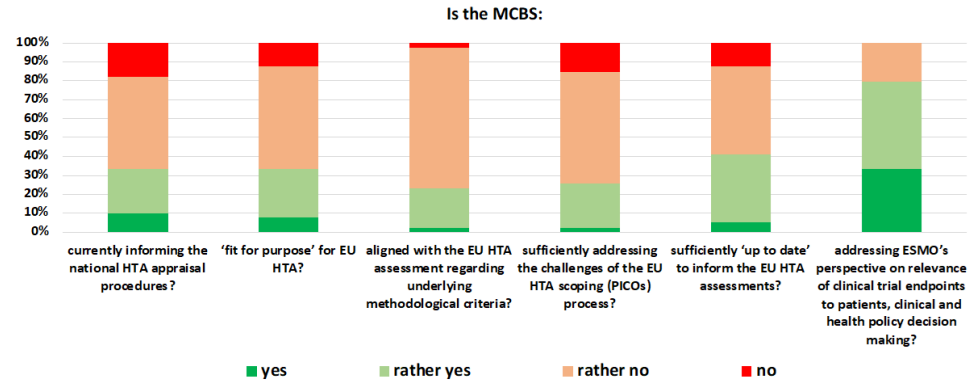

Figure 3: Percentage of respondents (of a total of n=39 who responded "yes" to the question if they are aware of the ESMO-MCBS) who responded "yes", "rather yes", "rather no" or "no" to the questions regarding specific aspects of the suitability of the ESMO-MCBS for (EU) HTA.

With the EU HTA process initially applying to oncology drugs and ATMPs, where Randomized Controlled Trial (RCT) data might not be available at the time of the assessment, the challenges of uncertainty and of having appropriate methodology to address this (data) uncertainty remain crucial[4, 5]. When asked about situations in which **'best-available evidence'** other than an RCT should be acceptable within an HTA JCA, the majority of respondents considered ethical considerations (84,8%), time considerations (78,3%), population details (100,0%) and the size of effects (87,0%) as relevant (including answers "yes" or "rather yes") criteria for such a decision (Figure 4).

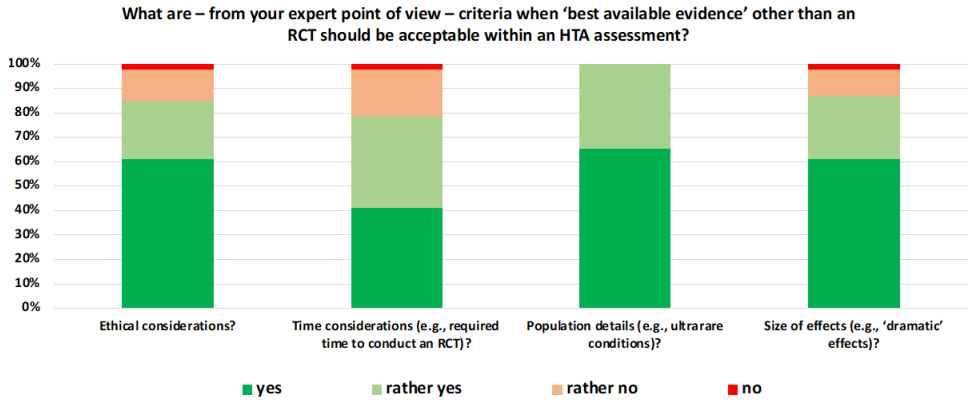

Figure 4: Percentage of respondents (of a total of n=46) who responded "yes", "rather yes", "rather no" or "no" to the questions regarding criteria for situations when 'best-available evidence' other than an RCT should be acceptable within an HTA assessment.

Clinical Professional Associations are evidently crucial stakeholders and experts in their field and should be involved in any HTA. For the evolving EU HTA process their involvement is explicitly mentioned in the Regulation[1] and in Deliverable D7.2 - Guidance for the interaction with patient representative, healthcare professional and other experts of the EUnetHTA 21 consortium[6]. However, the interim results of this EAA research survey reveal differing opinions on the specific aspects of the role of clinical societies in the EU HTA process. Further, there appears to be an opportunity for improvement on the applicability and suitability of clinical guidelines and the ESMO-MCBS in HTA assessments. The involvement of clinical experts in EU HTA will be crucial so that the assessments will reflect the "real clinical value" of new health technologies, beyond mere methodological analyses.

This will be highly relevant in cases such as, but not limited to, ATMPs, targeted oncology medicines and ultra-rare conditions where RCT data might not be available for the assessment. The survey respondents are largely in agreement that ethical and time considerations, population details and size of effects are important criteria to determine that 'best-available evidence' other than an RCT should be acceptable within an HTA JCA, however currently the handling of non-RCT data differs greatly between regulatory and HTA bodies[7]. Further multi-stakeholder discussions leading to clear definitions and guidance will be needed to approach this controversial topic.

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 Fall Convention 2023 in Barcelona. 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 the role of clinical associations, guidelines, the ESMO-MCBS, and the concept of best-available evidence in EU HTA.

1 The European Parliament and the Council of the European Union. 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. Official Journal of the European Union L 458/1.22.12.2021. 2021. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32021R2282&qid=1678205652192. Accessed 7 March 2023.

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Outlook EAA Spring Convention 2024 at Erasmus University in Rotterdam

Type I and II error in HTA: Finding the right balance is a challenge far beyond clinical trial statistics.

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Managing uncertainty is a key challenge both, in any bedside clinical decision as well as in any public health decision. Sir Austin Bradford Hill, one of the grandfathers of medical statistics, therefore suggested to carefully consider 9 different criteria to study association to address underlying uncertainty[1]. The related two archetypes of error in medical statistics are [2]:

- a type I error (alpha error), usually referred to as a 'false positive error' i.e., an untrue rejection of the null hypothesis and
- a type II error (beta error), the failure to reject an untrue null hypothesis i.e., a 'false negative' error.

For example, in an oncology clinical development program, a type I error occurs when the primary study endpoint of Overall Survival indicates a superiority of the test medicine versus the comparator while there is none – i.e., non-justified optimism. Reversely, a type II error refers to a situation when the study results indicate lack of superiority albeit, the test medicine does, in reality, achieve an increase in median overall survival i.e., non-justified skepticism.
Those errors may always occur and can never be completely excluded. However, 'inferential statistics' teaches how to minimize the potential for error and how to manage the related uncertainty. Mostly, the level of alpha and beta errors are interrelated i.e., a decrease of alpha is linked to an increased risk of beta error and vice versa. Finding the right balance across the two errors is therefore a key task of any clinical trial planning.

Those archetypes of clinical trial errors may be generalized far beyond clinical trial statistics. Almost any clinical, regulatory, health technology and payer decision situation is challenged by those two errors:

- Clinicians should neither provide patients with medicines that are not beneficial nor withhold medicines that are beneficial to their patients either from an efficacy or side effect perspective. I.e., clinicians are aiming for the right balance across over- and undertreating their patients.
- Similarly, regulators are striving to minimize the risk of falsely assigning a positive risk-benefit ratio vs falsely rejecting the authorization of a medicine with an untrue negative risk-benefit ratio.
- Health Technology Assessment Bodies are charged with the determination of the additional benefit of a new technology versus the existing standard of care. To the benefit of patients, they should neither assign an additional benefit where there is none, nor falsely suggest no additional benefit for an innovative medicine that in reality has an additional benefit.
- Finally, payers should neither provide additional funding for medicines or procedures that don't provide an incremental benefit and value to the patients nor withhold payment for medicines or procedures that provide an advance for patients unless the costs are not sustainable for the healthcare system.

Finding the right balance between those two archetype errors is therefore an essential challenge for almost any healthcare - related decision. Similarly, §3 of the preamble of the EU HTA regulation states that: 'HTA is able to contribute to the promotion of innovation, which offers the best outcomes for patients and society as a whole and is an important tool for ensuring proper application and use of health technologies.'[3] Hence, innovative technologies that offer best outcomes should be promoted by HTA while those that don't offer best outcomes should not be promoted.

In April 2024 only few months are left before the commencement of the first EU HTA level JCA procedures. At EAA's spring convention we will investigate the type I (falsely embracing non-beneficial innovation) and type II (falsely rejecting beneficial innovation) error potential of the developing EU HTA Assessment from the key stakeholders' and collaborators' perspective: patients, clinicians, regulatory, HTA bodies, payers, and health policy makers.

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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
Handelsregister Basel CHE-344.552.708
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Publication Series
EAA Convention Proceedings Volume 4, 2023

ISSN
2813-3390

Editorial Work
Jörg Ruof, Elaine Julian

Images/Copyrights
Title Image: Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS), Barcelona, Spain

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 and endorsed & funded by:
Springer Healthcare, Abbvie, AstraZeneca, Bayer, Novartis, Roche, Sanofi , Seagen, vfa, leem and efpia.

EAA Publication

Van Haesendonck L., Ruof J., Desmet T., Van Dyck W., Simoens S., Huys I., 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., Julian E.: The role of stakeholder involvement in the evolving EU HTA process: Insights generated through the European Access Academy's multi-stakeholder pre-convention questionnaire. JMAHP 11, 1, (2023). doi: https://doi.org/10.1080/20016689.2023.2217543

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

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