Challenges and Opportunities in Implementing the EUNETHTA21 Methodological Guidelines in the Context of EU HTA Regulation: Perspectives from Different Stakeholders on Different Markets (FRANCE, ITALY, AND POLAND)

Poster HTA293

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Background

EU HTA Regulation 2021/2282 and Joint Clinical Assessment (JCA)/ Joint Scientific Consultation (JSC) methodological and procedural guidelines

The EU Health Technology Assessment (HTA) Regulation 2021/2282 came into force in 2022 EU HTA with the objective of establishing a collaborative framework for the coordinated assessment of health technologies, reducing duplication of work, facilitating exchange of information among EU member states (MSs) and aiming to improve patient access across the EU.[1] The Regulation mandates JCA for oncology products and ATMPs from January 2025, for orphan products from January 2028 and for all other medicinal products from January 2030.

JCA is scientific analysis of the relative effects of medicinal products against chosen parameters selected by applying the Population Intervention Comparator Outcome (PICO) framework. The scientific analysis should include consideration of the degree of certainty of the relative effects, considering the strengths and limitations of the available evidence. The assessment culminates with the publication of the JCA Dossier submitted by manufacturers and the JCA Reports summarizing all those aspects, excluding any value judgments, which remain within the scope of Member States (MSs).[1] Furthermore, MSs hold the responsibility for conducting local HTA and making reimbursement decisions. During the local pricing and reimbursement (P&R) process, they should consider the evidence submitted for JCA and may request supplementary data. However, it's important to note that they cannot duplicate requests for the same data that was previously submitted for JCA. Methodological and procedural guidelines covering methodology, JCA/CA, JSC, and transversal activities have been developed by the EUnetHTA21 Consortium, which has finished to operate on September 16th 2023. All guidance documents will be adopted by the Coordination Group and assessors and co-assessors to conduct JCA and JSC starting from 2025. The methodology proposed for JCA is expected to influence the future HTA and P&R processes at MS level at different levels.

Objectives

This study aims to assess challenges and opportunities from various stakeholders' perspectives (i.e., HTA bodies [HTAb], manufacturers, and others) in France, Italy, and Poland, in respecting and applying the EUNnetHTA21 proposed methodological and procedural guidelines in the Context of EU HTA Regulation.

Methods

The EU HTA Regulation methodological and procedural guidelines developed and published from March 2022 to September 2023 by EUnetHTA were downloaded and reviewed **(Table 1)**.[2] Since the EU HTA Regulation will be applied to medicinal products, medical devices and *in vitro* diagnostic medical devices, only the guidelines for medicinal products were considered for this analysis.

Table 1. EUnetHTA methodological and procedural deliverables for JCA and JSC published between March 2022 and September 2023 for medicinal products

Deliverable ID	Date of finalization
D4.2 – Scoping process	September 2022
D4.3	
D4.3.1 – Practical guideline direct and indirect comparisons	November 2022
D4.3.2 – Methodological guideline on direct and indirect comparisons	July 2022
D4.4 – Endpoints	January 2023
D4.5 – Applicability of evidence	November 2022
D4.6 – Validity of clinical studies	November 2022
D5.1 – JCA/CA Submission Dossier Template	September 2023
D5.2 – JCA/CA Assessment Report Template	November 2022
D5.3	
D5.3.1 – Procedural guideline for appointing assessors and co-assessors	June 2022
D5.3.2 – HTAb technical expert working	July 2022
D7.1 – Guidance for the interaction between HTD and HTA (for JCA and JSC)	September 2022
D7.2/3	
D7.2 – Guidance on patient & healthcare professional involvement	November 2022
D7.3 – Input templates	November 2022
D7.5 – Guidance for identifying and handing conflict of interest (COI) and declaration of interest (DOI) – and EUnetHTA confidentiality agreement (ECA) forms	March 2022

We also identified and reviewed local pharmaceutical legislation and HTA guidelines published between January 2016 and September 2023 in place at the time of the analysis in France[3,4], Italy[5,6,7], and Poland[8,9]. This allowed us to conduct a qualitative analysis of how the JCA process could potentially impact the timeline and methodology used for local HTA assessments.

The qualitative analysis considered the perspectives of multiple stakeholders involved in HTA and P&R decisions, including HTAbs, manufacturers, and future JCA assessors and co-assessors

Results

In total, 14 final deliverables for JCA published by the EUnetHTA Consortium were found and reviewed **(Table 1)**. In addition, 6 local legislation and guidelines published by HTAbs and regulators in France, Italy and Poland were identified and reviewed for the analysis.

Considering different stakeholder perspectives and aspects of the local P&R process in France, Italy and Poland, three main areas of challenge were identified.

Compatibility and requirements for Early Access Programs (EAPs) and JCA

- The introduction of JCA is aimed at reducing the time to access for medicinal products to patients in the EU, but other forms of early access and funding to innovations, such as EAPs, might be impacted.
- In France, the Early Access pre-Marketing Authorisation (MA)[3] requires submission of clinical evidence before MA is granted for the medicinal product, creating a potential overlap with evidence submitted for JCA or a difference in comparators between EAP and JCA.
- A similar situation could happen in Italy where early access of medicinal products through Law 648/96[7] requires the submission of a light Dossier to AIFA with the executive summary of the clinical conditions and clinical studies supporting the P&R request.

Framework for local P&R Dossier and regulation adaptations needed

- Adaptation of evidence required in local dossiers will be necessary since any evidence submitted for JCA cannot be submitted locally. On one hand, this should decrease the time for manufacturers to prepare local dossiers, but on the other hand, it requires local HTAbs and legislation to update guidelines and templates for the local P&R dossiers. In addition, new pharmaceutical legislation should also be developed and provided at the MS level.
- In Italy[6] and Poland, manufacturers are required to submit the Dossier through an online platform with a rigid framework based on the official guidelines and legal regulations. Therefore, without a change in the guidelines and local regulations, manufacturers will still be required to submit a full Dossier after 2025, potentially leading to an overlap between data submitted for JCA and for the local Dossier, as well as duplication of work. Similar situation could happen in France where HAS provides a framework and explanation of evidence requirements for the local Dossier.

Difference in methodologies applied for JCA and local HTA

- Lastly, appointed JCA assessors and co-assessors may be required to assess the evidence twice (during JCA and at local level) using different methodologies.
- This could be relevant for Poland which applies local AOTMiT HTA methodological guidelines from 2016[8]. As an example, we can highlight differences in the scales used to assess the quality of data from non-randomized or single-arm studies. In Poland, the questionnaire for the internal validity of Non-Randomised Studies (NRS) is recommended for the assessment of non-randomized trials, and for single-arm studies, the NICE scale is used. However, per EUnetHTA proposed guidelines, the risk of bias in non-randomized controlled trials should be assessed using ROBINS-I to enable proper evaluation by MS. Additionally, in EUnetHTA proposed guidelines, we can also find some general information indicating that given the lower importance of uncontrolled trials (e.g., single-arm trials) for relative effectiveness assessment and HTA, it is considered unnecessary to propose any formal rules for assessing the risk of bias of single-arm trials.

Discussion

- The EU HTA Regulation aims to expedite patient access and reduce duplication of work among member states. Achieving this goal requires HTA agencies and regulators to:
  - Define what evidence should be included or excluded in the JCA process and how it integrates into local decisions;
  - Consider not only traditional P&R procedures but also early access programs, with input from HTD stakeholders;
  - Determine the optimal timing for starting local P&R procedures, balancing patient needs and assessment complexities.
- These considerations are pivotal to the successful implementation of the EU HTA Regulation, aligning local practices with overarching objectives.

Conclusions

The EU HTA Regulation aims to reduce access time, prevent duplication of work for HTAb, and enhance pharmaceutical product accessibility for EU patients. Local HTAb and manufacturers, between Global Corporate Team and Affiliate Teams, must proactively prepare and adapt local regulations on reimbursement procedures to facilitate EU-level work and to avoid delays in local processes.

References

1. European Union. Regulation (EU) 2021/2282
2. EUnetHTA21, Joint HTA Work (link)
3. HAS, EAP Doctrine, 2022 (link)
4. HAS, Transparency Commission Doctrine 2023 (link)
5. AIFA, Dossier Guideline 2019 (link)
6. AIFA, Pharmaceutical Legislation 2019 (link)
7. AIFA, Law 648/1996 (link)
8. AOTMiT, HTA Guidelines Version 3.0 2016 (link)
9. Act of May 12, 2011, on the reimbursement of medicines, special dietary foods, and medical devices (2023 amendment) (link)

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