A Comparison of the Acceptability of Evidence in the New Joint Clinical Assessment and Nine European Union Countries

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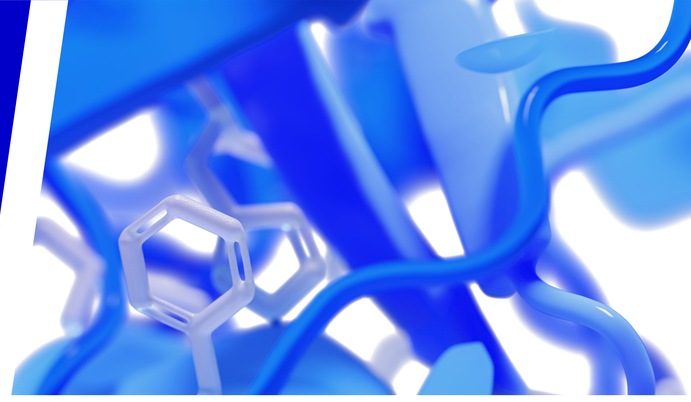

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Introduction

- The new EU Regulation on Health Technology Assessment (EU HTAR) aims to harmonize HTAs across Europe and improve patient access to innovative medicines. In 2025, Joint Clinical Assessment (JCA) will become a mandatory process for health technology developers (HTDs) seeking reimbursement in the EU, starting with oncology drugs and advanced therapy medicinal products (ATMPs)
- Guidance published by the Methodological and Practical Guidance (MPG) subgroup outlines the evidence requirements for addressing the PICOs (Population, Intervention, Comparator, Outcome) in the JCA dossier
- Thus far, MPG guidelines have been published on direct and indirect comparisons[1-2], outcomes for JCA[3], reporting requirements for multiplicity issues and subgroup, sensitivity and post hoc analyses in JCAs[4], criteria defining medicinal products subject to JCA[5], and validity of clinical studies[6]. Further guidance is expected throughout 2024
- However, a high level of uncertainty remains as to how the EU JCA will influence and impact HTA processes at a local level, which would subsequently impact Pricing and Market Access (P&MA)
- Therefore, this study evaluated and compared the acceptability of different types of evidence and methodologies across nine EU member states in relation to MPG guidance, as well as acceptance of HTDs' PICO justifications by HTA bodies **(Figure 1)**
- The aim was to understand potential challenges in the interpretability and usefulness of the JCA report in local decision-making by HTA bodies, particularly for oncology

Methods

Figure 1. Comparison of evidence acceptability approach

Step 1

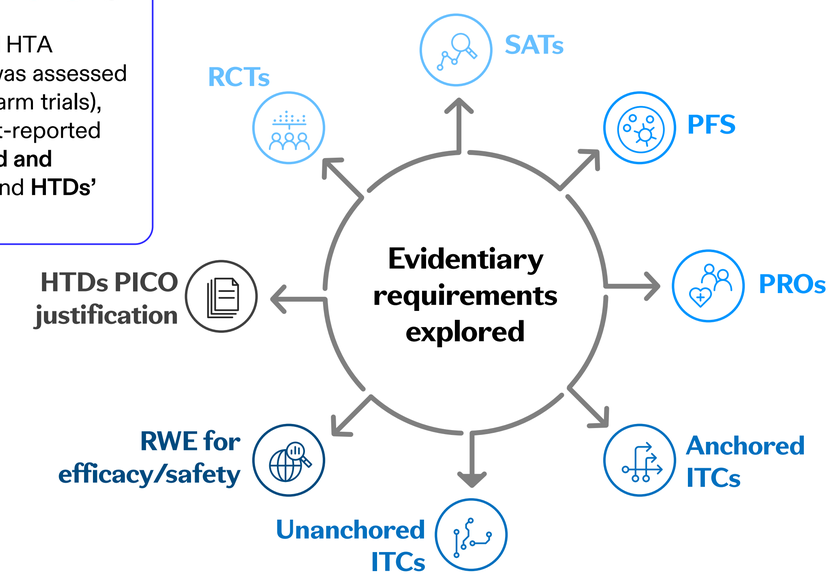
Review of evidentiary requirements from published MPG guidance[1-6] and HTA guidance[8-17], for JCA and nine EU countries, respectively. Acceptability was assessed for **pivotal trial data** (RCTs – randomized controlled trials, SATs – single-arm trials), selected **RCT endpoints** (PFS – progression-free survival, PROs – patient-reported outcomes), **indirect treatment comparisons (ITCs) using RCTs: anchored and unanchored**, and using **real-world evidence (RWE) for efficacy/safety**, and **HTDs' PICO justification**

Step 2

Validation of evidentiary requirements with **country P&MA subject matter experts (SMEs)**

Step 3

Validation of evidentiary requirements **with EU4 ex-payers**, from DE, FR, ES and IT



Abbreviations: RCT - Randomized Controlled Trial, SAT – Single-Arm Trial, PFS – Progression-Free Survival, PRO – Patient-Reported Outcomes, – PROs, ITC - Indirect Treatment Comparison, RWE – Real-World Evidence, HTD – Health Technology Developer, PICO – Population, Intervention, Comparator, Outcome

Results

- The evidence requirements for the EU JCA dossier, as outlined in the published MPG guidance[1-6], are equivalent to those of the most stringent HTA guidelines of HTA agencies, such as G-BA[8]/ IQWiG[9] and HAS[10], and are more restrictive than many local HTA guidelines of HTA agencies, e.g., TLV[11], AOTMiT[13] **(Figure 2)**

EU JCA

- RCT data are the gold standard for evaluating causal relationships between interventions and outcomes because randomisation eliminates much of the bias inherent to other designs[6,7]
  - There is no specific critique for an open-label design; the impact of study design on internal study validity, including blinding, should be assessed by the ROB-1 tool[6]
- The acceptability of other evidence types and methodologies varies:
  - Acceptability of SATs as pivotal trials, unanchored ITCs, and RWE is low, while the acceptability of anchored ITCs is case-dependent[1-6]
    - Unanchored ITCs should be considered only with access to full Individual Participant Data (IPD) from all studies to facilitate full assessment of heterogeneity, which is likely to be challenging
- Even for common surrogate endpoints, such as PFS, acceptability is low; they can be accepted if validated, although there is no clear guidance on the validation criteria[1-6]
- PROs are acceptable; ideally the outcomes should be long-term or final where possible; the HTD must provide enough information for each MS (member state) to appraise the validity, reliability and interpretability of each measurement instrument[1-6]
- Acceptance of HTDs' PICO justification[a] is expected to be variable/case-dependent; the published MPG guidance outlines the expected evidence requirements for JCA

Member states

- Acceptability of evidence and methodologies varies across MS:
  - Traditionally, Germany and France are less accepting of non-RCT evidence[8,9,10,18,19]
  - SATs are not accepted in Germany (except for orphan drugs)[b] and France, and have an overall low acceptance in other countries[8-19]
  - Except for Germany, PFS is typically accepted across MS if its use is justified, i.e., if time necessary to collect Overall Survival (OS) data is unrealistic; acceptability of PFS also depends on data maturity, statistical power, and relevance to clinical practice[20-22]
  - PROs measured in RCTs are generally accepted across MS; however, in France, HAS prioritizes alpha risk control, leading to high rejection rates of PROs[10]
  - Acceptability of unanchored ITCs using RWE to demonstrate efficacy/safety is case-dependent or low in most MS[8-19]
  - HTD rationale for the evidence approach to meet specific PICO criteria is accepted by some MS (FR, PL, ES, IT, PT, SK) as part of their national process; while there is low acceptability in DE and NL e.g., in DE, PICOs are defined by G-BA who can request additional information from the HTD if necessary

Note: a - 'HTD PICO justification' refers to the JCA/HTA body's willingness to accept manufacturers rationale for the evidence approach to meet specific PICO criteria; b – In Germany, even for orphan drugs, comparative data from RCTs or anchored ITCs are required to receive a quantifiable added benefit. If only a SAT is available, a non-quantifiable added benefit will be granted by law once the orphan drug is approved

Figure 2. Acceptability of different evidence types and methodologies varies across EU JCA and local HTA bodies in 9 EU member states

	Pivotal trial data		RCT endpoints		ITCs using RCTs		ITCs using RWE	
	RCT	SATs	PFS	PROs	Anchored ITCs	Unanchored ITCs[f]	RWE for efficacy/safety[g]	HTDs PICO justification[h]
JCA	Accepted	Not accepted	Not accepted	Accepted	Variable/ case-dependent	Not accepted	Not accepted	Variable/ case-dependent
DE	Accepted	Low[a]	Low[c]	Accepted	Variable/ case-dependent[e]	Low	Low	Not accepted
FR	Accepted	Low[a]	Variable/ case-dependent[d]	Variable/ case-dependent	Variable/ case-dependent	Not accepted	Not accepted	Accepted
SE	Accepted	Variable/ case-dependent	Accepted	Accepted	Accepted	Variable/ case-dependent	Variable/ case-dependent	Variable/ case-dependent
NL	Accepted	Variable/ case-dependent	Variable/ case-dependent	Accepted	Variable/ case-dependent	Variable/ case-dependent	Not accepted	Not accepted
PL	Accepted	Variable/ case-dependent	Accepted	Accepted	Accepted	Variable/ case-dependent	Accepted	Accepted
PT	Accepted	Not accepted	Accepted	Accepted	Accepted	Accepted	Variable/ case-dependent	Accepted
SK	Accepted	Not accepted	Accepted	Accepted	Accepted	Not accepted	Not accepted	Not accepted
ES	Accepted	Variable/ case-dependent	Variable/ case-dependent	Accepted	Variable/ case-dependent	Not accepted	Not accepted	Accepted
IT	Accepted	Not accepted	Variable/ case-dependent	Accepted	Variable/ case-dependent	Not accepted	Not accepted	Accepted

Notes: a – Accepted for orphan drugs; in DE, for SATs a non-quantifiable added benefit will be granted as the added benefit is granted by law for orphan drugs once approved. b – Generally acceptable, however the open-label design will introduce bias and may lead to non-acceptance of results for endpoints that could be potentially highly influenced (e.g., PROs and safety). c – G-BA would always state that radiographically measured PFS would not be accepted, whereas symptomatic progression could be acceptable, however, in practice, progression events are usually measured by RECIST, therefore by radiographic. d – in FR, PFS is accepted if time necessary to collect OS data is unrealistic but, in the end, there will be a re-assessment with OS data and PFS will not impact the final opinion. e – Practice shows that most of the times the rigorous requirements cannot be fulfilled (e.g., ITC evidence not only for efficacy but also for safety and PRO required, which is often not available from published sources) or the power of the ITCs is too low to demonstrate any statistically significant advantages. f – Some acceptability concerns regarding unanchored comparisons, with a preference for full individual patient data for matched adjusted indirect comparisons/ simulated treatment comparisons; g – Role of RWE in JCA is not yet clear, RWE is generally used in EU4 HTA submissions to inform e.g., epidemiology, to support pricing negotiations or to support clinical evidence base; h – 'HTD PICO justification' refers to the JCA/HTA body's willingness to accept manufacturers rationale for the evidence approach to meet specific PICO criteria

Acceptability:
Accepted
Variable/ case-dependent
Low
Not accepted

Explanation of the acceptability categories:
'Accepted' – Evidence/methodology is typically accepted without major exceptions; it is generally recognized and endorsed as a valid and reliable approach across the majority of HTA agencies and contexts
'Variable/ case-dependent' – Evidence/methodology type is accepted in certain cases; its acceptability may vary based on specific circumstances or criteria, and it may be contingent upon the context in which it is being applied
'Low' – Evidence/methodology type is typically not accepted; it is generally viewed as lacking credibility or reliability
'Not accepted' – Evidence/methodology type is outlined in the HTA/MPG guidance as not accepted; it is generally disregarded as a valid approach
Evidence/methodology outlined in Figure 2 was placed in the acceptability categories based on 1) Review of evidentiary requirements from published MPG guidance[1-6] and HTA guidance[8-17] for JCA and nine EU countries, respectively; 2) Validation of evidentiary requirements with country P&MA subject matter experts (SMEs); 3) Validation of evidentiary requirements with EU4 ex-payers, from DE, FR, ES and IT. For more information on sources, see **Figure 1.**

Payer insights

- With the lack of formal publications from European HTA bodies detailing the local implementation of the EU JCA, exact influence and impact of EU JCA on MS evidence acceptability remains uncertain
- EU4 ex-payers believe EU JCA may modify the evidence standards for those HTA agencies who are more receptive to change (see below)
  - EU JCA could potentially reduce acceptability of evidence types where the acceptability is currently higher than in the EU JCA, e.g., AIFA in Italy, AEMPS in Spain
- Limited EU JCA influence is expected for HTA bodies traditionally less accepting of new evidence types, e.g., non-RCT evidence (see below)
  - High G-BA evidence requirements are not expected to change; TLV already has a high acceptability of new evidence types, e.g., anchored ITCs, which is expected to be maintained
  - Payers thought HAS evidence requirements could potentially change in the long run

- Overall, HTA bodies which are traditionally less accepting of non-RCT evidence, are expected to be less likely to adapt their requirements, e.g., G-BA
- TLV already has a high acceptability of non-RCT evidence types, which is expected to be maintained

In FR, EU JCA could influence the acceptability of ITCs and PROs in the long run

EU JCA could potentially reduce acceptability of evidence types where the acceptability is currently higher, e.g., AIFA, AEMPS

Conclusions

- Our results show, based on currently available MPG and local HTA guidelines, that EU JCA evidence requirements are comparable to some of the most stringent EU HTA agencies, i.e., G-BA/ IQWiG and HAS
- There is a lack of consensus on how evidence submitted for EU JCA will be utilised at the MS level
- Initially, evidence and methodology acceptability by local HTA agencies may not change; however, over time, the standards and criteria set forth by the EU JCA are likely to shape the way evidence is considered and accepted
- EU JCA is expected to raise the evidence standards for some HTA agencies i.e., AIFA and AEMPS
- However, EU JCA is expected to have limited impact to countries whose HTA agencies are less accepting of non-RCT evidence e.g., G-BA
- Evidence standards of TLV, which already have a high acceptability of non-RCT evidence types, is expected to be maintained
- Although historically perceived as less open to adopting changes, HAS evidence requirements could potentially change in the long run

Implications

- EU27 MS will submit their evidence needs in the form of PICOs that they deem necessary to be able to assess the clinical effectiveness for their national context. For EU JCA, these PICOs will be consolidated to produce a final scope which could include multiple PICOs
- Stringent evidence requirements, coupled with the high expected number of PICOs in the final JCA scope, represent significant challenges for HTDs
- Relying solely on RCT data is unlikely to address the expected high number of PICOs, therefore, ITCs will likely be needed
- The lack of acceptance of PFS as surrogate endpoint for OS represents an additional challenge, given it is accepted by regulatory agencies[19-21] and has been widely used by the oncology clinical community
- These challenges create the risk of HTDs not fully addressing PICOs in the final scope. In cases where evidence is not provided for certain PICOs, justification for the omission should be included in the dossier in the form of an objection handler
  - The definition and implications of what would be deemed 'an incomplete dossier' have yet to be clearly defined. Specifically, it remains uncertain whether failing to address certain PICOs, such as due to ITC feasibility challenges, would result in the discontinuation of the JCA, potentially impacting local HTA processes
  - Therefore, it is evident that some degree of flexibility on submitted evidence and methodologies from assessors/co-assessors will be necessary to ensure ongoing patient access to new medicines
- It is crucial for HTDs to realign their market access strategy and preparations in response to the evolving HTA environment. Market access teams should leverage the Joint Scientific Consultation (JSC) to proactively identify and inform PICOs early, and highlight complex cases to ensure adequate resources and time are allocated for developing the necessary robust evidence packages, whilst monitoring the evolution of EU evidence requirements

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Abbreviations, disclaimers, funding

Abbreviations:
AEMPS – Agencia Española de Medicamentos y Productos Sanitarios, AIFA – Agenzia italiana del fármaco, AOTMiT – Agencja Oceny Technologii Medycznych i Taryfikacji, ATMPs – Advanced Therapy Medicinal Products, EU – European Union, G-BA – Gemeinsamer Bundesausschuss, HAS – Haute Autorité de santé, HTAR – Health Technology Assessment Regulation, HTD – Health Technology Developer, INFARMED – Autoridade Nacional do Medicamento e Productos de Saude I.P., ITCs – Indirect Treatment Comparisons, IQWiG – Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, JCA – Joint Clinical Assessment, MPG – Methodological and Practical Guidance, NIHO – Národný inštitút pre hodnotu a technológie v zdravotníctve, SMEs – Subject Matter Experts, PFS – Progression-Free Survival, PICO – Population, Intervention, Comparator, Outcome, P&MA – Pricing & Market Access, PROs – Patient-Reported Outcomes, RWE – Real-World Evidence, RCT – Randomized Controlled Trial, SAT – Single-Arm Trial, TLV – Tandvårds- och läkemedelsförmånsverket, ZIN – Zorginstituut Nederland

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