Simulating PICOs to Predict Evidence Requirement Implications of the EU Joint Clinical Assessment: Learnings from 24 Case Studies

HTA300

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Introduction

Need for internal planning

With **several products currently undergoing** JCA and no JCA reports available yet, **HTDs must proactively interpret the official MPG** to **adjust internal planning**

JCA PICO scope

A key JCA objective is to establish the **JCA PICO scope** with input from all **EU MS** (PICO survey)[1]; HTDs have limited involvement

Short submission timeframe

Once the JCA assessors share the consolidated PICOs, HTDs must provide appropriate evidence requested **within 60 (accelerated EMA procedure)** or **100 (standard EMA procedure) days**

Anticipation of JCA PICOs

HTDs need to **anticipate the PICO scope early** and **submit the requested evidence** on time or **provide a strong justification for not addressing PICOs**

PICO simulation case studies

24 PICO simulations (January 2022 – April 2025) were conducted following latest MPG[2-6] on the JCA scoping process **(Figure 1)** to support HTDs predict the PICO scope and inform their evidence generation strategy

Methods

Figure 1: PICO Simulation Methodology

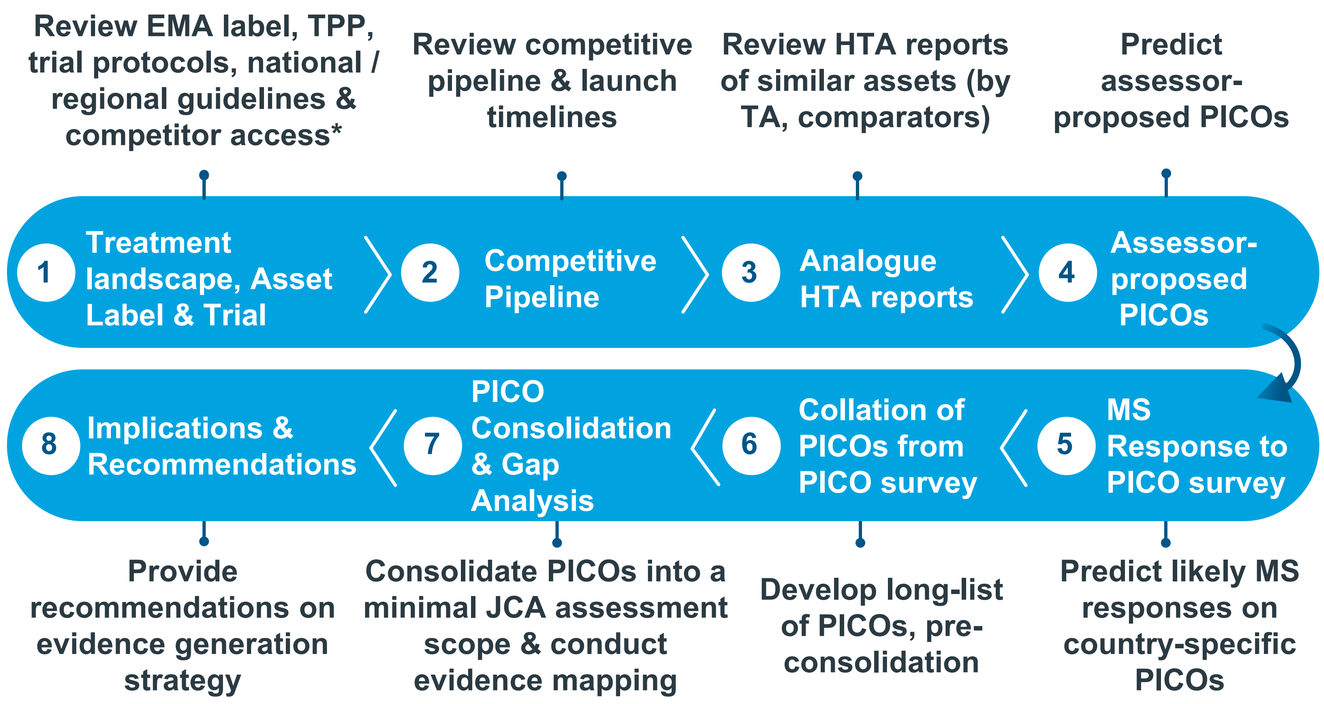

Figure 1. *Step-by-step methodology for PICO simulation exercises. Latest MPG[2-6] on the JCA scoping process and learnings from PICO exercises conducted by the HTA CG were followed. *Off-label products could also be requested during JCA depending on the TA/current SoC considerations*

Results

- PICOs were simulated for **21 oncology products**[7] and 1 genetic disorder; 2 of these were ATMPs and 2 also had orphan drug status**.** Indications included **breast cancer** (n=5), **lung cancer** (n=7), **haematological cancers** (n=5), other **solid tumours** (e.g., gastric, prostate, etc., n=6) and a genetic disorder (n=1)
- The number of MS to predict the country-specific response to the PICO survey ranged from **5 – 15 MS**. A **base case** (most-likely scenario) and a **'worst case'** (following the most rigorous interpretation of the latest MPG on the JCA scoping process, alongside considerations such as EMA label interpretation and competitive landscape) were developed for each asset, where applicable
- The **median number of PICOs** was **9 and 17 in the base- and worst-case scenarios**. Findings were in line with PICO exercises carried out by the JCA Subgroup (**Table 1**)[8-10]
- Notably, **subgroup analyses were also requested across all PICOs by the JCA Subgroup**; however, the **list of outcomes was not as extensive or descriptive as initially anticipated**, alleviating some concerns regarding the scope of required evidence
- The minimum number of analyses for the base case ranged from **35 to 720** and **270-3,663** for the worst case, pending ITC feasibility assessments. As seen in **Figure 2**, **most PICOs (67%) would require an ITC**
- The TA with the highest number of PICOs was **breast cancer** (16 in base, 25 in worst case), while other oncology indications had similar number of PICOs (~10 in base case) (**Figure 3**)

Figure 2: Per PICO evidence mapping

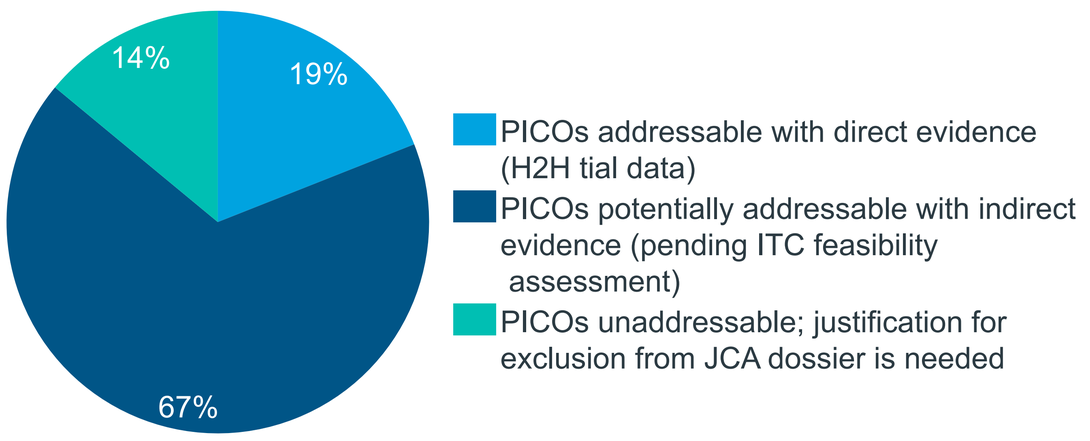

Figure 2. *Distribution of PICOs (N= 170 PICOs, base case) across case studies (N=24) by per PICO evidence mapping and gap analysis (i.e., addressable, potentially addressable, unaddressable)*

Table 1: Number of PICOs across case studies & JCA Subgroup exercises

	Base Case Median (range)	Worst Case Median (range)	JCA Subgroup exercises Median (range)[8-10]
Populations	6 (1 – 16)	9 (3 – 21)	7 (3 – 7)
Comparators	8 (4 – 18)	12 (6 – 23)	7 (6 – 16)
Outcomes	27 (17 – 54)	34 (17 – 111)	26 (20 – 39)
PICOs	9 (5 – 21)	17 (5 – 88)	13 (7 – 13)

Table 1. *Summary of median and range outputs of the total number of PICOs, populations (full EMA label + subpopulations), comparators and outcomes for the base- and worst-case across case studies (n=24), including a comparison to PICO exercises carried out by the JCA Subgroup (n=3)*

Figure 3: Median number of PICOs by TA

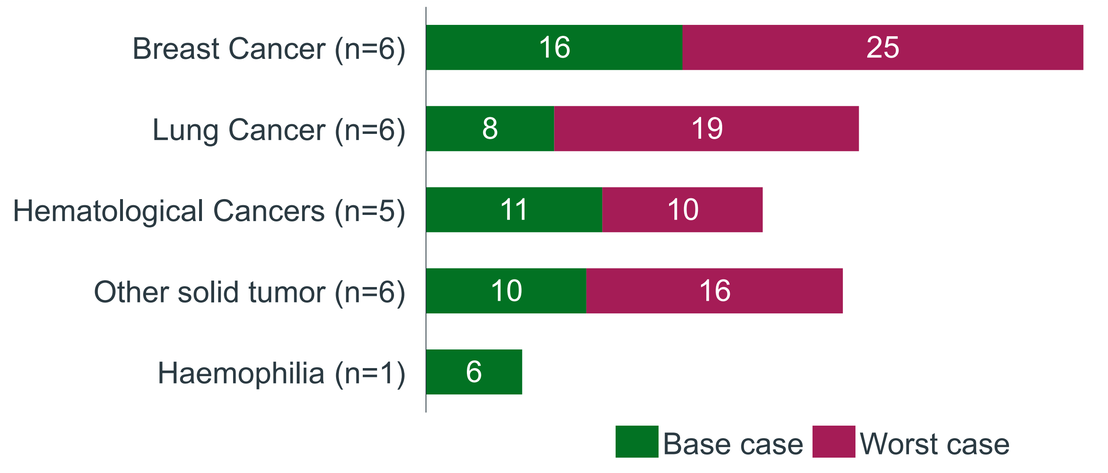

Figure 3. *Median number of PICOs by TA in the base and worst cases across PICO simulation case studies (N=24); Haematological cancers include lymphomas, leukaemia's, MDS & myeloma indications; Other solid tumours include prostate, bladder, gastric/GEJ, glioma & HNSCC*

Conclusions and implications

1. Our findings for the number of predicted PICOs are in line with the **PICO simulation exercises for medicinal products** carried out by the **JCA Subgroup** (PICOs range 7-13), demonstrating the robustness of our analysis and early insights from ongoing JCAs. For products launching in complex treatment landscapes where SoCs vary by MS, the anticipated **number of PICOs and associated analyses is anticipated to be high**.
2. The majority of PICOs (up to ~80%) require **ITCs to demonstrate comparative effectiveness vs all comparators requested,** or **strategic justification for exclusion from the JCA dossier** when not feasible, imposing a **significant burden on HTDs** to deliver comprehensive evidence within tight timelines.
3. Considering the limited input from HTDs in the JCA scoping process and the high number of expected JCA PICOs, **early anticipation of PICO requirements** (i.e., as early as Phase 1 development) is crucial to better inform **pivotal trial design and overall evidence generation strategy** (i.e., planning for ITCs, RWE, etc.)[11].
4. **Learnings from the ongoing JCA processes in 2025** indicate that, **in addition to a high number of PICOs, subgroups** aligned partly with clinical trial stratification factors **will be requested across all PICOs where data is available. This further increases the analysis burden, making early planning and prediction of PICO subpopulations and potential subgroup analyses crucial.**
5. HTDs should also **iteratively review and refine their PICO predictions** to account for updates to the treatment landscape (i.e., changes to treatment guidelines), and broader asset strategy (i.e., EMA label updates).

References: 1 – Regulation (EU) 2021/2282 on Health Technology Assessment; EUR-Lex; Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021; 2 – Guidance on the Scoping Process – European Commission; Guidance on the Scoping Process V1.0; 3 – Guidance on Outcomes for Joint Clinical Assessments adopted on 10 June 2024; 4 – Guidance on Validity of Clinical Studies adopted on 19 September 2024; 5 – Guidance on Direct and Indirect Comparisons adopted on 8 March 2024; 6 – Guidance on Reporting Requirements for Multiplicity Issues and Subgroup, Sensitivity and Post Hoc Analyses in JCAs adopted on 10 June 2024; 7 – van Engen A, et al. 2004. HTA6 Predicting PICOs to Prepare for Joint Clinical Assessment: Learnings From 19 Case Studies. Value in Health, 27(12), S353; 8 – European Commission JCA Subgroup PICO Exercise 1 – Durvalumab (Imfinzi®); 9 – European Commission JCA Subgroup PICO Exercise 3 – Adagrasib (Krazati®); 10 – European Commission JCA Subgroup PICO Exercise 5 – Etranacogene dezaparvovec (Hemgenix®); 11 – Tanner S, et al. 2024; The EU Health Technology Assessment Regulation Halo Effect: Are Cross-Functional Teams Ready? J Mark Access Health Policy. 2025;13(1):3; **Abbreviations:** CG – Coordination Group; EMA – European Medicines Agency; GEJ – Gastroesophageal Junction; H2H – Head-to-Head; HNSCC – Head and Neck Squamous Cell Carcinoma; HTD – Health Technology Developer; ITC – Indirect Treatment Comparison; JCA – Joint Clinical Assessment; MDS – Myelodysplastic Syndrome; MPG – Methodological and Practical Guidance; MS – Member State; PICO – Population, Intervention, Comparator, Outcomes; RWE – Real-world Evidence; SoC – Standard of Care; SLR – Systematic Literature Review; TA – Therapy Area; TPP – Target Product Profile; **Disclaimer:** The authors declare no conflicts of interest. This research received no external funding.