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EU HTA
MULTIPLE PICO CRITERIA

ADVANTAGE OR OBSTACLE FOR DRUG MANUFACTURERS?

2023

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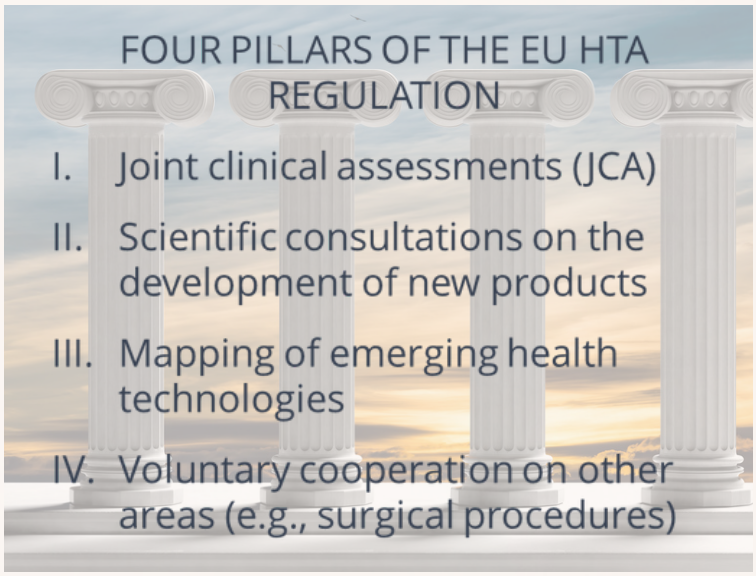
EU HTAR: A BRIEF RECAP

The EU HTA regulation (EU HTAR) was adopted by the European Parliament in December 2021 and aims to reduce duplication of assessments by member states.

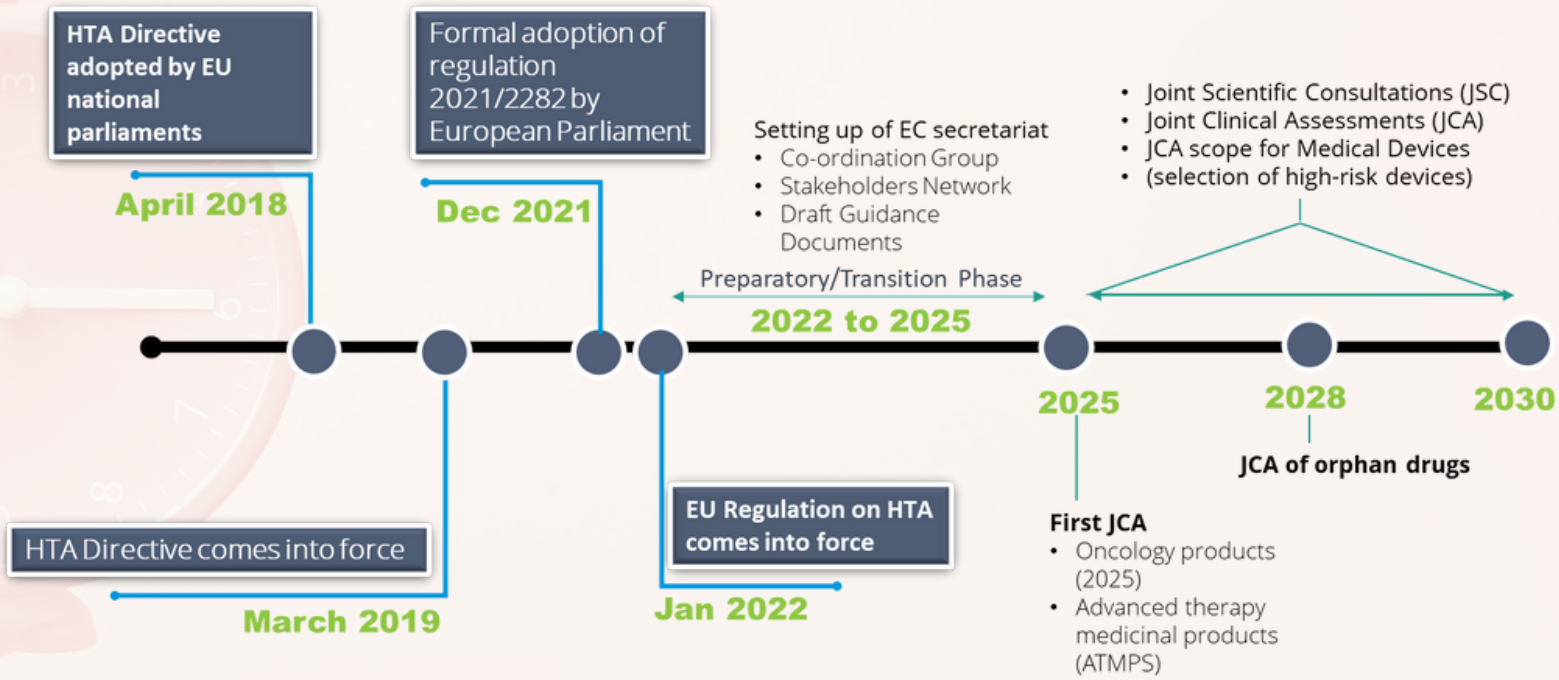
EU Level Joint Activities

JCA and JSC for drugs, diagnostics and high-risk medical devices



EU Member State Activities

- Added value/benefit assessments
- Pricing and reimbursement decisions
- National HTA criteria (e.g., rare disease, disease severity)



JCA Joint Clinical Assessment
JSC Joint Scientific Consultation

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What is a PICO ?

- PICO is a key part of evidence-based medicine (EBM). It recommends to formulate clinical questions in terms of the problem/population, intervention, comparison, and outcome.
- Most HTA assessments are performed based on a PICO framework. National HTA bodies define PICO criteria during the scoping review or horizon scanning stage (if applicable) just before commencing any assessment.
- PICO criteria are framed according to national health policy priorities , following systematic reviews and are the first initiating step of any HTA.
- In the new EU HTA process, the JCA secretariat will regularly facilitate PICO surveys among EU member state HTA bodies.

Population

- Corresponding to the treatment indication of interest

Intervention

- Usually a single intervention is preferred

Comparator(s)

- Single or multiple and may also include standard of care or background therapies

Outcome

- Single or multiple outcomes may be relevant for a given intervention (e.g. mortality, morbidity, qualityof life etc,)

For more information about PICOs please see Huang X,.et al., (2006). "Evaluation of PICO as a knowledge representation for clinical questions" . AMIA Annu Symp Proc. 2006: 359–63.

Why are PICO criteria so important for HTA ?

- PICOs and associated methods in evidence demonstration are core elements for HTA assessments; key requirements are specifically outlined at national level to define appropriate comparators for assessing additional clinical value or clinical benefit of any new health technology.
- Manufacturers already include PICO relevant evidence in national HTA dossiers based on criteria stipulated by HTA bodies.
- Please note that PICO criteria only help define appropriate comparators for a given intervention, the final outcome of any HTA is determined by comparative assessment after considering other factors such as quality and certainty of evidence and risk of bias.

Health policy question

PICO Questions

Specifies data requirements for manufacturers to include in HTA dossiers

Specifies assessment framework for HTA bodies

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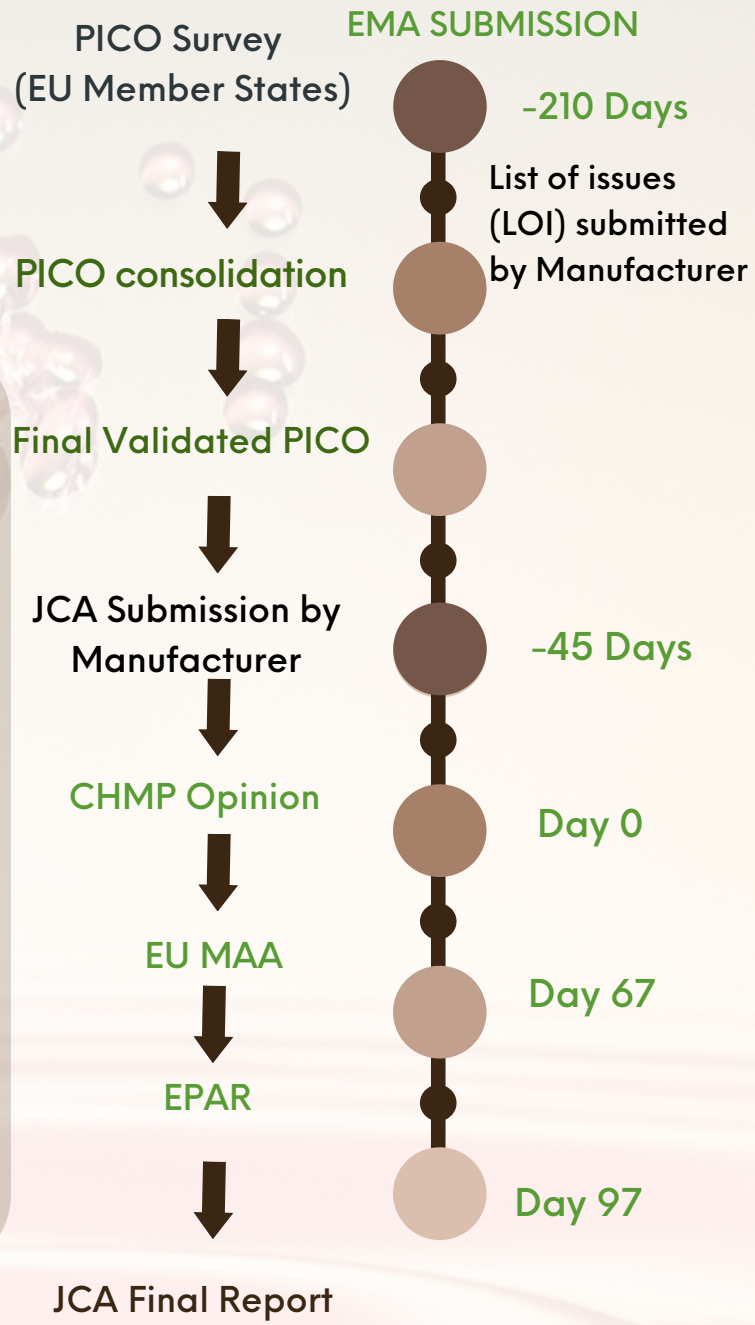
Why is everyone discussing the EU HTA PICO criteria ?

- EU member states with different HTA assessment priorities and required methods in evidence demonstration, differing treatment patterns, disease burden and unmet needs will require different PICO requirements and methods in evidence demonstration.
- Multiple PICO criteria will be consolidated across EU member states through a PICO survey process lead by the JCA secretariat.

- Consolidated PICO criteria from EU member states will be provided to manufacturers.
- All PICO questions and data requirements need to be addressed in the JCA dossier.

- PICO surveys for EU member states will be coordinated by the EU HTA JCA secretariat.
- No specific time span for completion of PICO consolidation activities is currently mandated in guidelines, however individual member states may use pre-existing scoping review procedures (for e.g. UK NICE scoping reviews are usually published within 24 months of regulatory approval).
- Rapid consolidation of multiple PICOs and achievement of maximum convergence is encouraged in the EunetHTA scoping guidelines but only time will tell how practically feasible this may be.



Please note that all EUnetHTA activities are a collaborative effort of the EUnetHTA consortium comprised of 13 EU member state HTA body representatives. The PICO scoping guidelines discussed ihere have been jointly authored by the Gemeinsamer Bundesausschuss, [G-BA], Germany, Haute Autorité de Santé, [HAS], France, Institut für Qualität und Wirtschaftlichkeit im Gesundheitsw esen, [IQWIG], Germany and Zorginstituut Nederland, [ZIN], The Netherlands

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How will multiple PICO criteria be decided for EU HTA ?

EU member states define PICO parameters according to their national legal and procedural requirements.

1 PICO SURVEY

- Clear and consistent definition per indication
- Both full and sub-populations identified

- One per assessment where applicable
- Consideration for variations in standard of care (i.e., background therapy)

- Single or multiple
- Maybe other treatments (e.g., physiotherapy) with/without background therapy

- Single or multiple
- Outcomes may be conceptual (e.g., HRQoL without specific instrument name)
- Specified without desired effect measures or any type of value judgements

Key Stakeholders: HTA bodies from EU member states along with patient and clinical experts (who provide inputs for PICO development) and the EU HTA JCA secretariat

PICO survey form: An example

Parameter	PICO 1	Other PICO(s) (if needed) *In case of multiple PICOs, separate columns should be made for the different aspects.* *If PICOs are similar with regard to some parameters (e.g., no differences between the PICOs on outcomes), the cells should be merged between adjacent identical columns.*
Population	Relevant population for the assessment scope [see 'Population' (Subsection 3.1)]	
Intervention	Intervention to be assessed [see 'Intervention' (Subsection 3.1)]	
Comparator(s)	Expected comparators. In the case of several comparators, 'OR' or 'AND' separation must be chosen [see 'Comparators' (Subsection 3.1)]	
Outcomes	Expected outcome (effectiveness, safety, quality of life) [see 'Outcomes' (Subsection 3.1)]	
Additional information	See 'Additional information' (Subsection 3.1)	

2 PICO CONSOLIDATION AND VALIDATION

- Divergent PICO requirements will be assessed and consolidated.
- EU HTA assessor and co-assessors will juxtapose population requirements per member state with comparators and outcomes to create multiple PICOs
- Attempts will be made to achieve the fewest number of PICOs by further clarification from member states, if timelines permit

Key Stakeholders: Joint clinical assessment (JCA) secretariat and Committee for Scientific Consistency and Quality (CSCQ)

Final validated multiple PICO criteria

	PICO 1	PICO 2	PICO 3	PICO 4	PICO 5
P	Full licensed indication	Full licensed indication	Full licensed indication	Subpopulation A	Subpopulation B
C	Comparator 1 OR Comparator 2[14]	Comparator 3	Comparator 4	Comparator 1	Comparator 3
O	All outcomes	All outcomes	All outcomes	All outcomes	All outcomes

3 JCA Dossier

- The final validated PICO criteria define the data requirements for the JCA dossier.
- Re-analyses of clinical data sets (indirect comparisons) will be needed to address multiple PICO requirements.

Key Stakeholders: Manufacturer medical, market access and statistical analyses teams

JCA dossier Patient characteristics and clincal evidence

- Chapter 1: PICO 1 (comparator 1 or 2)
- Chapter 2: PICO 2 (comparator 3)
- Chapter 3: PICO 3 (comparator 4)
- Chapter 4: PICO 4 (comparator 1, subpopulation A)
- Chapter 5: PICO 5 (comparator 1, subpopulation b)

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A few additional words about the EU HTA PICO consolidation processes: an anticipated bottleneck

Consolidation of multiple PICO requirements from EU member states would be complicated. Current guidelines outline a 4 step process for arriving at a consensus (please see graphics below). However, how effectively and efficiently this process may work in the real world is yet to be tested.

Example of STEP 1 of PICO consolidation process

Member State 2			
Population(s)	Full licensed indication	Subpopulation A	Subpopulation B
	Comparator(s) Could use any of ~~/ all required~~	Comparator(s) Could use any of ~~/ all required~~	Comparator(s) ~~Could use any of /~~ all required
	Comparator 1	Comparator 1	
	Comparator 2		
	Comparator 3	Comparator 3	Comparator 3

1.
- Per Member State, set apart PICO
- Indicate if ALL comparators are needed or ONLY ONE comparator is required (AND/OR scenarios)

2.
- Juxtapose Member state PICO requirements per population

Example of STEP 2 of PICO consolidation process

Full licensed indication		
Member State 1	Member State 2	Member State 4
Comparator(s) Could use any of ~~/ all required~~	Comparator(s) Could use any of ~~/ all required~~	Comparator(s) ~~Could use any of~~ / all required
Comparator 1	Comparator 1	
Comparator 2	Comparator 2	
	Comparator 3	Comparator 3
		Comparator 4

3.
- Select Comparators per population

Example of STEP 3 of PICO consolidation process

Full licensed indication		
Member State 1	Member State 2	Member State 4
Comparator(s) Could use any of ~~/ all required~~	Comparator(s) Could use any of ~~/ all required~~	Comparator(s) ~~Could use any of~~ / all required
Comparator 1	Comparator 1	
Comparator 2	Comparator 2	
	Comparator 3	Comparator 3
		Comparator 4

4.
- Create final consolidated PICO table

Example of STEP 4 FINAL VALIDATED PICO FOR EU HTA

	PICO 1	PICO 2	PICO 3	PICO 4	PICO 5
P	Full licensed indication	Full licensed indication	Full licensed indication	Subpopulation A	Subpopulation B
C	Comparator 1 OR Comparator 2[14]	Comparator 3	Comparator 4	Comparator 1	Comparator 3
O	All outcomes	All outcomes	All outcomes	All outcomes	All outcomes

What does this mean for drug manufacturers and their future plans for EU market access ?

FOR PRICE AND REIMBURSEMENT NEGOTIATIONS

- **New ways of determining the price potential of a new treatment may become applicable**. As JCAs are used at the national level of each member state for determining added value or clinical benefit ratings, the choice of PICOs will influence the clinical value ratings to a great degree. Further, pricing assessments may require additional evidence post-JCA. Hence a full shift to value based price potential calculation is possible.

FOR EARLY STAGE MARKET ACCESS ACTIVITIES (3 to 5 years ahead of EU launch date)

- **Earlier engagement through joint scientific advice processes** will be needed as mismatch between clinical evidence and PICO questions can affect HTA bodies assessment of validity and applicability of evidence for their national value, pricing and reimbursement decision making.
- **Increased knowledge gathering activities** about unmet needs and (sub) population compositions from different EU member states will be essential for meeting multiple PICO data requirements..
- **Additional analytical capabilities** for indirect treatment comparisons, post-hoc analyses and RWE will be required to address multiple PICOs.
- Drug manufacturers need to **stay alert for more updates** as EU member state HTA, pricing and reimbursement bodies begin to consider JCA reports for country specific decision making. More updates from member state HTA bodies are anticipated between September 2023 (when the EUnetHTA service contract comes to an end) and January 2025 (first full JCA will be commissioned).
- Market access teams need to **rethink drug launch strategies** to also consider member states that may have not been priority markets in the past. This is an inescapable component of the EU HTA multiple PICO scoping process for JCA submissions from 2025.

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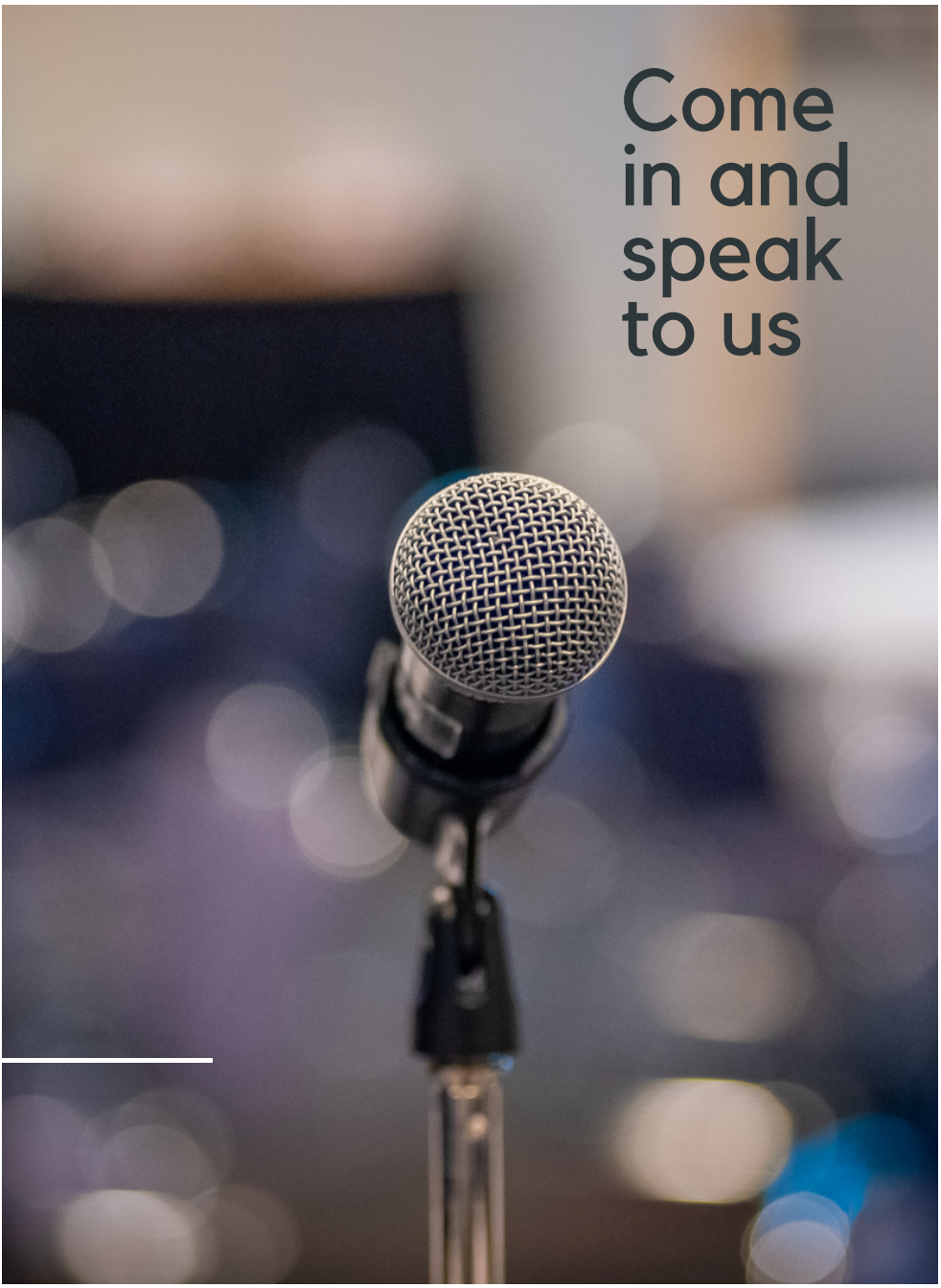

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Materials used in this document were drawn from the following sources:
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2. Julian et al. Health Economics Review (2022) 12:54 https://doi.org/10.1186/s13561-022-00402-x
3. https://www.eunethta.eu/wp-content/uploads/2022/09/EUnetHTA-21-D4.2-practical-guideline-on-scoping-process-v1.0.pdf