Overlaps and differences in the PICO criteria between the different EU countries

Gallinger P[1], Bonduelle D[1], Plantör S[1], Schmalhofer C[1], Mattern F[1], Streicher S[1], Troubat A[2], Van Engen A[3]
[1]IQVIA Commercial GmbH & Co. OHG, Munich, Germany
[2]IQVIA France, Paris, France
[3]IQVIA the Netherlands, Amsterdam, the Netherlands

OBJECTIVES

The Regulation (EU) 2021/2282 on health technology assessment (HTA) entered into force in January 2022 and will apply from January 2025 onwards. The aim of the HTA Regulation is to improve the availability of innovative technologies for EU patients and to increase efficiency through joint clinical assessment (JCA).

The process foresees that, according to principals of evidence-based medicine, the PICO scheme (Population, Intervention, Comparator(s), Outcomes) are used and defined at national level. The PICO scheme is then to be addressed in the JCA.

The JCA process runs parallel to the approval process of the European Medicines Agency (EMA) (Fig. 1). A major hurdle in the process is the agreement of the HTA bodies on a PICO scheme for the evaluation of the new active substance. Each Member State submits a PICO scheme which will be discussed and, if possible, harmonized in a consolidation meeting.

The objective of this analysis was to evaluate the overlaps and differences in the PICO scheme between different EU countries.

METHODS

We compared the PICO scheme of individual EU countries, specifically Czech Republic, France, Germany, Italy, the Netherlands, Poland and Spain. First, we compared the current methods of HTA of the EU countries according to the applicable regulations. In addition, we surveyed local HTA experts using a standardized questionnaire.

RESULTS

We identified both overlaps as well as differences between the EU countries regarding the PICO scheme (Tab. 1). Our analysis shows that the PICO scheme must meet specific national requirements for the seven countries analyzed. For example, the relevant patient population can either be the population according to EMA approved indication, the study population, or the population to be reimbursed depending on the country. Equally, country differences are shown in the relevant comparator(s) because the standard of care depends on country specific guidelines and reimbursed drugs. Concerning the outcomes, the currently accepted endpoints differ between the countries. Complete consistency of requirements across all seven countries considered could not be identified for any PICO scheme.

CONCLUSION

Per current EU HTA scoping process there will not be an aligned PICO scheme. This leads to several challenges such as the generation of an extensive amount of data within a short time frame. Another challenge is the potential lack of overlap between the pivotal clinical trials and national PICO scheme in terms of comparators; this challenges the direct comparison. Considering the narrow time frame of the JCA process running parallel to the approval process, an alignment of PICO scheme requirements should be considered as early as possible to ensure a complete and beneficial JCA.

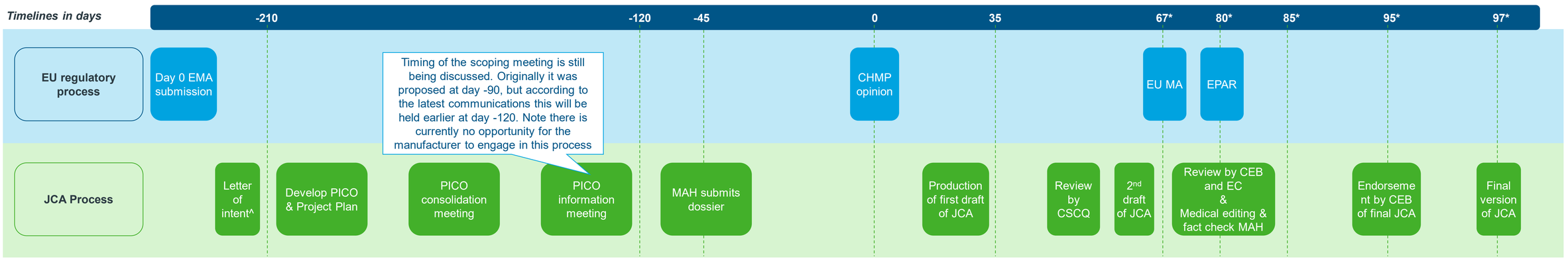

Figure 1: JCA Timelines. *Note: Dependent on regulatory timelines; ^Submission of a LOI by the manufacturer is part of the EUnetHTA 21 process, but it is not clear whether this will be retained in 2025. Abbreviations: MA: Marketing Authorization; MAH: Marketing Authorization Holder; PICO: Population, Intervention, Comparator(s), Outcomes; CSCQ: Committee for Scientific Consistency And Quality; CEB: Consortium Executive Board , EC: European Commission.

HTA agency	AEMPS[1]	AIFA[2]	AOTMiT[3,4]	G-BA[5] / IQWiG[6]	HAS[7,8]	SUKL[9]	ZIN[10]
Population							
Is the **relevant patient population for the HTA** the therapeutic indication as per SmPC?		Population according to specific reimbursement request	The MAH specifies the population to be assessed within the therapeutic indication.		Study population should be consistent with claimed population to be reimbursed	The MAH specifies the population to be assessed within the therapeutic indication.	Population can deviate from the SmPC indication if more narrow; according to specific reimbursement request and study population
Does the HTA agency request **separate analyses by subpopulation** in case of potentially important differences (e.g. clinical effectiveness, comparator)?	Yes, separately for predefined subgroups with proven greater/ equal / lower benefit in RCTs	Yes, population heterogeneity should be explored in subpopulation analyses	Yes, depending on clinical effectiveness or costs	Yes, if different comparators for subpopulations	HAS only assess subgroup analysis that has been planned in the protocol	Yes, depending on clinical effectiveness or costs	Yes, relevant (sub)groups identified by for example physicians
Intervention							
Are **posology and administration method** based on SmPC**?**					SmPC and the results of trials		
Are **diagnostic tests, prognostic factors or risk factors** decided by the HTA agency?	No specific recommendation	If appropriate, to identify patients eligible for treatment	If relevant in patient funnel and/or cost-effectiveness			If relevant in patient funnel and/or cost-effectiveness	Depending on Dutch practice
Is the **background therapy** applied in the clinical trial accepted for HTA?	No specific recommendation	Only if similar to the national context	Only if similar to the national context	Only if similar to the national context	Only if similar to the national context	Only if similar to the national context	Only if similar to the national context
Comparator(s)							
Is **standard of care** the only **criteria** for the HTA agency to determine the **comparator**?	Comparator in the RCT should represent standard of care. If trial does not represent the standard of care, the election of the comparator is based on cost-effectiveness/efficiency criteria	Standard of care in clinical practice: 1) according to national or international guidelines 2) The treatment or combination of treatments that are utilized the most in the Italian clinical practice (including off-label treatments)	1) Reimbursed 2) Standard of care in clinical practice	1) Approval in indication 2) For non-drug treatments: reimbursed by SHI 3) Preferably drug with an additional benefit 4) Standard according to current state of medical knowledge (clinical guidelines, SLRs) Orphan drugs: Comparator from pivotal study	Must be situated at the same level of the therapeutic strategy as the drug evaluated and must be intended for the same patients	1) Reimbursed 2) Standard of care in clinical practice	Standard of care: 1) in clinical practice, or 2) according to clinical guidelines
Best supportive care if no standard of care is available?	No specific recommendation				In oncology, first-line treatment, comparators should include supportive care	Without a reimbursed therapy, “watch and wait” is comparator	
Are **off-label therapies** considered under special conditions?	Off-label therapies are not commonly accepted		Off-label therapies are not commonly accepted	Only if there are no approved drugs in the therapeutic indication	Therapies used off-label or under early access or compassionate access may be considered	Off-label therapies are not commonly accepted	Off-label therapies are not commonly accepted
Outcomes							
What are the **main categories** for clinically relevant endpoints: **Morbidity, mortality, quality of life and safety?**	Main categories are morbidity and mortality	Morbidity, mortality, QoL, and additional category: Added therapeutic value				Depends on life-threatening vs. non-life-threatening disease	Clinically relevant endpoints depend on the burden of disease and indication (in consultation with physicians). Quality of life and safety are always considered
Does the **follow-up time** depend on type of disease?	No specific recommendation	No specific recommendation		For chronic diseases at least 24 weeks	And clinical context		No specific recommendation
Are **validated surrogates** accepted?	Accepted, if final clinical endpoints are not available		Accepted, if direct endpoints cannot be presented	Surrogates are rarely accepted	Only if link to clinical endpoint of morbidity and mortality is demonstrated	Accepted, if direct endpoints cannot be presented	Accepted as supporting evidence

Table 1: Overlaps and differences between the EU countries in the PICO scheme. Color coding: Yes (green), partly (yellow), no (red). Abbreviations: AEMPS: Spanish Agency of Medicines and Medical Devices; AIFA: Italian Medicines Agency; AOTMiT: Agency for Health Technology Assessment and Tariff System; G-BA: Federal Joint Committee; HAS: Haute Autorité de Santé; IQWiG: Institute for Quality and Efficiency in Health Care; SmPC: Summary of product characteristics; SUKL: State Institute for Drug Control; ZIN: National Health Care institute.

Acknowledgements:

Ariane Batscheider (IQVIA Commercial GmbH & Co. OHG, Munich, Germany);
Bogdan Falkiewicz and Michaela Tauchmanová (IQVIA Czech Republic, Prague, Czech Republic);
Daniel Callejo Velasco (IQVIA Spain, Madrid, Spain);
Max van Wijk and Pauline Pasman (IQVIA the Netherlands, Amsterdam, the Netherlands);
Pailina Rolska-Wójcik (IQVIA Poland, Warsaw, Poland);
Alessia Tettamanti, Duccio Urbinati and Gloria Lombardi (IQVIA Italy, Milan, Italy).

References:
1. https://www.sanidad.gob.es/en/profesionales/farmacia/IPT/docs/20200708.PNT_elaboracion_IPT_CPF8Julio.pdf
2. https://www.aifa.gov.it/documents/20142/1283800/Linee_guida_dossier_domanda_rimborsabilita.pdf
3. https://www.aotm.gov.pl/en/guidelines/
4. https://isap.sejm.gov.pl/isap.nsf/DocDetails.xsp?id=WDU20111220696
5. https://www.g-ba.de/downloads/62-492-2905/VerfO_2022-05-19_iK_2022-08-17.pdf
6. https://www.iqwig.de/methoden/general-methods_version-6-1.pdf
7. https://www.has-sante.fr/upload/docs/application/pdf/2021-03/doctrine_ct.pdf
8. https://www.has-sante.fr/plugins/ModuleXitiKLEE/types/FileDocument/doXiti.jsp?id=c_1280594
9. https://www.sukl.cz/leciva/sp-cau-028
10. https://www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg

Poster presented at Virtual ISPOR Europe 2022 on 6. November – 9. November 2022; Presentation Code: HTA259
For further information please contact: IQVIA | Real-World Insights | Doreen.Bonduelle@iqvia.com