The difference between PICO evaluation across Australia, EU4 and UK

HTA47

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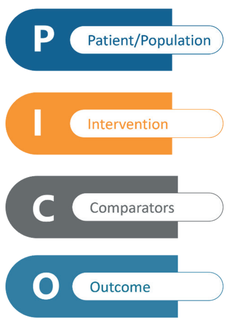
Background and Objectives.

The **Regulation (EU) 2021/2282** on health technology assessment (HTA), which will take effect in 2025, aims to enhance cooperation among EU countries in clinically assessing new health technologies. The goal is to promote the efficient use of health system resources while respecting national competences. This regulation introduces **Joint Clinical Assessments (JCA)** of medicinal products, establishing rules to ensure timely EU-level assessments of new medicines, involving or consulting relevant experts.

The starting point for the JCA is the **scoping process,** where **PICO schemes (Population, Intervention, Comparator(s), and Outcomes)** are used to define the research questions for the assessment. In the context of **EUnetHTA (European Network of Health Technology Assessment),** these research questions are based on policy questions from the healthcare systems where the HTA report will be used. The assessment is not driven by available data but rather by an appropriate translation of policy questions into research questions during the planning phase. Thus, the research question (PICO) is pre-specified for each assessment. Given the diversity of healthcare systems across Europe, it is possible that different policy questions —and consequently different PICO schemes— are formulated for the same medical intervention by various partners.

A central question for pharmaceutical companies is how many different PICO schemes need to be addressed in a European benefit dossier and how reliably these schemes can be anticipated prior to the scoping process.

The objective of this analysis is to evaluate the overlaps and differences in PICO schemes not only across European countries but also by exploring the evaluation approaches in **Australia** and the **UK**.



Methods.

Health Technology Assessment (HTA) and Pricing & Reimbursement (P&R) assessments for **Australia, France, Germany, Italy, Spain,** and **the UK** were reviewed for two medicinal products:

- **Fetcroja**, a new-generation antibiotic (not yet approved in Australia)
- **Kimmtrak**, an orphan medicine approved in all countries analyzed

These medicines were selected to explore potential differences in European evaluations between an orphan medicine, which targets a narrower population, and an antibiotic, which is used in a broader patient population. The information used to define the **PICO (Population, Intervention, Comparator(s), and Outcomes)** was gathered from published HTA documents.

This analysis focused not on the outcomes of the assessments but rather on how each individual agency evaluated the medicines in the context of PICO schemes. The research was centrally coordinated by **Productlife Group Global,** with local research conducted by PLG's Market Access teams in each country.

Results.

For **Kimmtrak**, which is authorized for the treatment of a rare oncological disease, all the countries analyzed defined a similar **PICO** framework, with no restrictions on the eligible population, and consistent comparators and outcomes across regions.

- **Population**: The eligible population defined by all countries aligned with the EMA indication: "KIMMTRAK is indicated as monotherapy for the treatment of human leukocyte antigen (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma." None of the agencies placed restrictions on the population.
- **Intervention**: In all cases, the intervention was Kimmtrak.
- **Comparators**: There were slight differences in the choice of comparators.
  - **Australia** included all available treatments.
  - **Italy** and **the UK** considered only immunotherapies and chemotherapies.
  - **Germany** focused solely on immunotherapies.
  - **France** did not regard these therapies as relevant comparators.

	Comparators
Australia	1. Immunotherapy (pembrolizumab, ipilimumab, dacarbazine, nivolumab) 2. Radiation therapy (plaque radiation therapy, proton beam therapy, stereotactic radiation therapy) 3. Laser treatment (transpupillary thermotherapy)
France	1. Chemotherapy protocols (such as dacarbazine andfotemustine, etc.) 2. Immunotherapies (such as pembrolizumab, nivolumab and ipilimumab) These drugs are not considered clinically relevant comparators
Germany	1. Dacarbazine 2. Ipilimumab 3. Lomustin 4. Nivolumab 5. Pembrolizumab
Italy	1. Chemotherapy (fotemustine, BOLD scheme) 2. Immunotherapy (ipilimumab, pembrolizumab, nivolumab, ipilimumab + nivolumab)
Spain	Dacarbazine, ipilimumab o pembrolizumab (IMCgp100-202)
UK	Pembrolizumab, nivolumab and ipilimumab immunotherapies, and dacarbazine chemotherapy. No SoC.After consultation, the company updated its analyses to compare tebentafusp with pembrolizumab

Table 1: Kimmtrak' s PICO comparators

In terms of Outcomes, all countries primarily based their assessments on the results of the IMCgp100-202 study. However, there were differences in the specific outcomes emphasized:

Australia, Italy, Spain, and the UK focused mainly on efficacy endpoints such as Overall Survival (OS), Progression-Free Survival (PFS), Objective Response Rate (ORR), and adverse events.

France and Germany also considered health-related quality of life (QoL) as a key outcome in their evaluations.

In contrast to the relatively consistent PICOs observed for Kimmtrak, the PICOs for Fetcroja, an antibiotic with improved efficacy against resistant and difficult-to-treat pathogens, showed significant variability across countries:

- **Population**:
  - **Australia, Germany, Spain**, and **the UK** approved the use of Fetcroja only in cases where treatment options are limited.
  - **France** and **Italy** imposed further restrictions by specifying particular pathogens and their resistance mechanisms within the indication.

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	Population
Australia*	Fetcroja is indicated for the treatment of infections due to aerobic Gram -negative organisms in adults with limited treatment options.
France	Favourable opinion for reimbursement in the MA indication only as a last resort for the treatment of patients with infections due to multi -resistant Gram-negative bacteria (particularly in the event of Enterobacterales and Pseudomonas aeruginosa, with a KPC, oxacillinase or metallo-β-lactamase resistance mechanism [NDM, VIM, IMP]) and when the use of the other available options is not possible.
Germany	Fetcroja is used in adults for the treatment of infections caused by aerobic gram -negative pathogens when only limited treatment options are available.
Italy	Fetcroja is used in adult in-patients with severe infections sustained by: 1. Carbapenem-resistant Enterobacterales (CR) producing metallo-beta-lactamase (MBL). 2. Pseudomonas aeruginosa producing metallo-beta-lactamase (MBL) and non-fermenting Gram-Negative (GN) pathogens 3. Difficult to Treat (DTR): Pseudomonas aeruginosa carbapenem resistant (CRPA), Acinetobacter baumannii carbapenem resistant (CRAB) and Stenotrophomonas maltophilia , in the absence of other therapeutic options and according to the principles of optimising antibiotic use.
Spain	Reimbursement is restricted for the targeted treatment of infections caused by gram -negative microorganisms for which no other therapeutic alternatives are available, either due to resistance or intolerance. The pathogens in which, a priori, cefiderocol is most likely to provide specific value are Enterobacteriaceae and, to a lesser extent metallobetalactamase (MBL)-producing P. aeruginosa.
UK	Fetcroja is used in infections (Enterobacterales and Pseudomonas aeruginosa) confirmed to be caused by MBL of the following subtypes: NDM, VIM, IMP

Table 2: Fectroja's PICO population

* Fetcroja is not currently registered or reimbursed within Australia. Therefore, the following is an estimation of what the PICO would look like should Fetcroja be reimbursed

- **Intervention:** In all cases, the intervention was **Fetcroja.**
- **Comparators:**
  - **Spain** considered only new-generation antibiotics as comparators.
  - In contrast, the other countries included a broader range of available treatment options, though these options differed by country.

	Comparators		
Australia	1. Cefepime 2. Cefotaxime 3. Ceftriaxone 4. Ciprofloxacin	5. Norfloxacin 6. Tobramycin 7. Gentamicin 8. Nitrofurantoin	9. Amoxicillin-clavulanic acid 10. Doxycycline 11. Minocycline
France	1. Colistine méthane sulfonate sodique 2. Ertapenem 3. Meropenem 4. Temocilline These drugs are not considered clinically relevant comparators	5. Imipenem-cilastatin-relebactamPiperacillina/tazobactam 6. Imipenem-cilastatin 7. Tigecycline	8. Meropenem-vaborbactam 9. Ceftazidime-avibactam 10. Ceftolozane-tazobactam
Germany	Used as last line of treatment		
Italy	1. Amikacin 2. Gentamicin 3. Nitrofurantoin 4. Cotrimoxazole 5. Fosfomycin trometamol/ EV 6. Ampicillin-sulbactam	7. Meropenem 8. Colistin 9. Tigecycline 10. Ceftazidime-avibactam 11. Meropenem-vaborbactam	12. Ceftazidime-avibactam + aztreonam 13. Imipenem-cilastatin-relebactam 14. Ceftolozane-tazobactam
Spain	Imipenem/ cilastatin (for APEKScUTI) Best available alternative with a maximum of 3 antibiotics (CREDIBLECR) Meropenem (APEKSNP)		
UK	Enterobacterales 1. Tigecycline + colistin 2. Fosfomycin + colistin 3. Aztreonam + colistin 4. Aminoglycosides (gentamicin, amikacin, tobramycin)	Pseudomonas aeruginosa: 1. Fosfomycin + colistin 2. Fosfomycin+ meropenem	

- **Outcomes:**

  All countries primarily focused on the following key endpoints in their evaluations of Fetcroja:
  - Clinical cure
  - Microbiological eradication
  - All-cause mortality

Conclusion.

JCA subgroups, responsible for delivering Joint Clinical Assessment (JCA) reports, should aim to limit PICO frameworks to 2-3 per assessment. However, our research highlights that while a harmonized approach can be observed for orphan drugs, significant discrepancies arise with other treatments. The lack of alignment between different PICO schemes across European countries presents challenges for the JCA process. This misalignment may impact the evaluation timeline and make it difficult to address the specific needs of each nation, potentially delaying access to treatments.

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