HTA95

Predicting evidence requirement implications of the EU Joint Clinical Assessment (JCA) through a Population, Intervention, Comparator, Outcomes (PICO) simulation for two anticancer investigational medicinal products (IMPs)

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Plain language summary

Why did we perform this research?

Currently, regulatory approval for new medicines in the EU is determined by a single body, while their effectiveness, safety and cost-effectiveness is often assessed by individual countries using Health Technology Assessment (HTA) to determine if they will be reimbursed. From 2025, an EU-wide version of HTA, the Joint Clinical Assessment (JCA), will be mandatory for cancer products. It aims to harmonise HTA approaches, establish predictability of HTA outcomes, and avoid duplication of effort for submitting and reviewing evidence, to ultimately accelerate patient access to new medicines. This means processes need to evolve both for how countries evaluate products and how health technology developers (HTDs) prepare the evidence.

How did we perform this research?

During the JCA, the HTD will need to provide evidence of the product's effectiveness and safety in specific patient populations, and a comparison to existing products used for the same indications. We simulated those requirements for two investigational anticancer treatments from 14 EU countries to understand the number of analyses required and the implications for HTDs.

What were the findings of this research?

For each simulated product, there were multiple patient populations to consider as patient populations were often defined differently across countries. Moreover, as treatment availability differed by country, numerous existing products were identified which would require comparisons to be presented against. Finally, countries differed in the exact effectiveness and safety outcomes they deemed relevant. Combining all these led to a substantial number of analyses being required for each product.

What are the implications?

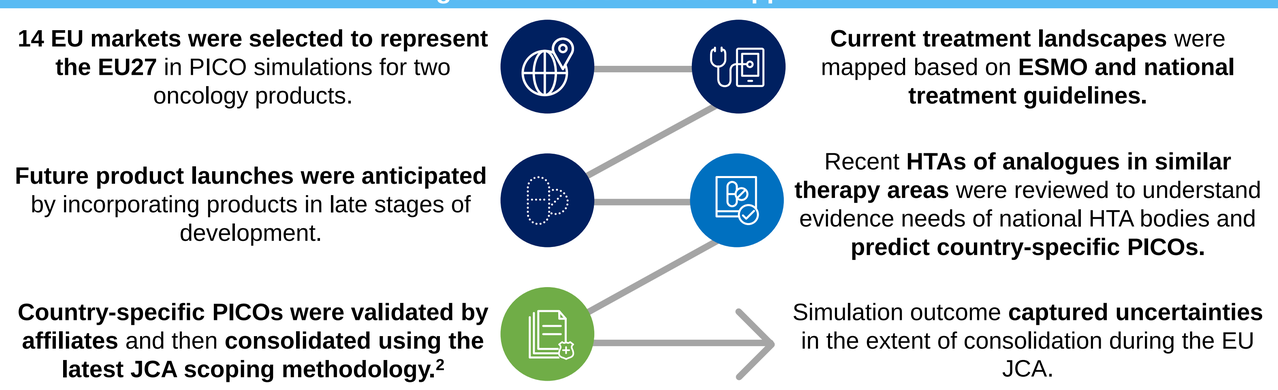
It may be difficult for HTDs to provide all the requested analyses in the timeframe required as part of this new process. Moreover, it is not yet clear how this new process will integrate into existing HTAs in EU member states (MS). This means more collaboration is required between key stakeholders to ensure this new process meets its objectives of enabling faster patient access to innovative medicines.

Introduction

- The EU JCA will introduce a new assessment after EMA marketing authorisation is obtained, but before national pricing & reimbursement discussions. A cornerstone of this is the PICO (population, intervention, comparator, outcome) framework, a systematic way to set the scope of the assessment, i.e., it provides a standard format for the definition of a research question.
- After the HTD submits the summary of product characteristics (SmPC) and clinical overview, the JCA assessors will propose PICO(s) and share them with MS for validation and input. These proposals are then consolidated by the assessors and shared with the HTD, who must provide the appropriate evidence within 100 days for a standard submission or 60 days for the accelerated process.[1]
- In this research, we aimed to simulate how this process would work for two medicinal products in development to understand the implications for all involved stakeholders (i.e., patients, HTDs, national HTA bodies).

Methods

Figure 1: PICO simulation approach



Results and implications

Figure 2: Overview of indications and outcomes for IMP1 & IMP2

- The two oncology products simulated are currently in Phase 3 clinical development and their key features are summarised below.
- To avoid revealing confidential information, the name of the IMPs, the diseases targeted by the IMPs, biomarkers and trial comparators of these IMPs are not reported.

	IMP1	IMP2
Indication	**2L monotherapy** for metastatic cancer X that has progressed after chemotherapy.	**In combination with chemotherapy** for previously untreated locally advanced/metastatic cancer Y, which expressed a specific biomarker.
Study Endpoints	**Primary outcome: Overall survival (OS)** Secondary outcomes: progression free survival (PFS), objective response rate (ORR), disease control rate (DCR), duration of response (DoR), and patient-reported outcomes (PROs).	**Primary outcome: OS** Secondary outcomes: PFS, ORR, DCR, DoR and PROs.

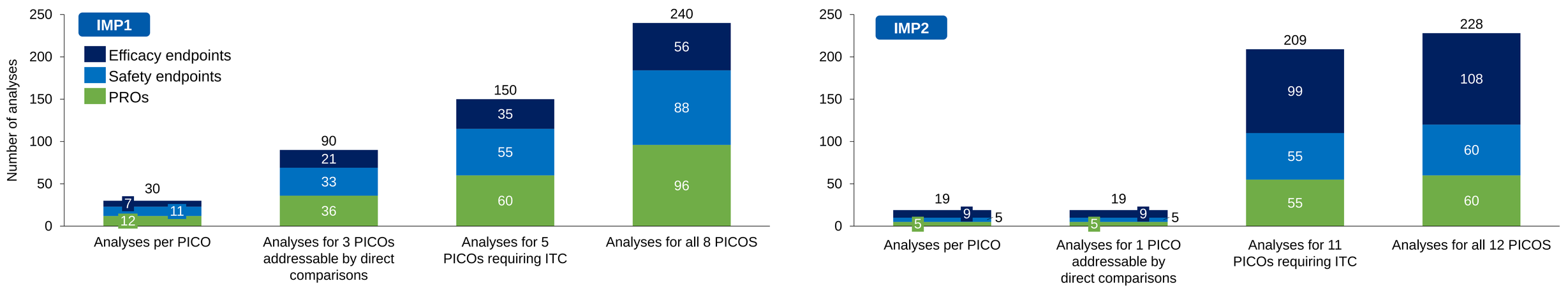
Figure 3: Simulated PICO scope based on 14 MS

	IMP1	IMP2
Population	EMA label + 3-10 subpopulations	EMA label + 4-8 subpopulations
Comparator	4-9 comparators	11-14 comparators
Outcomes	30-54 per PICO	19-32 per PICO
Number of PICOs	8-29	12-31
PICOs requiring ITCs	5-20	11-26
Number of analyses	240-1,566	228-992

Range shown reflects base case (lower number) to worst case (highest number)

- Both IMP1 and IMP2 are characterized by a complex treatment landscape:
  - ESMO and national guidelines characterize the IMP1 indication into at least 3 subpopulations based on the timing of disease progression. Up to 9 treatment regimens were identified that would serve as comparators for IMP1.
  - The treatment landscape for IMP2 distinguishes biomarker-negative/all-comers, biomarker-positive patients, and a small number of other biomarkers. Up to 14 treatment regimens were identified as relevant comparators for IMP2.
- After consolidation, a minimum of 8 and 12 PICOs were identified for IMP1 and IMP2, respectively, with an upper range of 29 and 31 PICOs.
- The ranges reflect a 'base case' and 'worst case', where the base case has lower numbers due to removal of PICOs requested by only one country, and merging different types of platinum-based chemotherapy. In addition, in the base case:
  - For IMP1, EMA and ITT populations were merged, as well as subgroups with small differences in time point of disease progression after 1L chemotherapy.
  - For IMP2: subgroups with similar biomarker-level cut-offs were merged.
- Depending on the final number of PICOs, up to 20 ITCs may be required to meet PICO requests for IMP1, and up to 26 ITCs for IMP2.

Figure 4: Predicted number and type of analyses required for IMP1 & IMP2 in base case scenario



- In the base case, we simulated that 240 analyses would be required for IMP1, and 228 for IMP2, across different efficacy, safety, and PROs outcomes.

Key implications for stakeholders

- **For HTDs**, extensive evidence requirements arise from the EU JCA, as demonstrated from the simulations of IMP1 and IMP2. This is compounded by the limited time of 100 days for the HTD to finalise the JCA dossier after receiving consolidated PICOs. To meet these timelines, PICOs will need to be predicted in advance, and analyses conducted prior to starting the EU JCA. These factors increase the risk of an incomplete EU JCA dossier, with as of yet unclear implications for national HTAs.
- **For MS,** there is high uncertainty. MS will need to provide input into the scoping process; however, there is a lack of consensus on how evidence collected for the JCA report will be utilised in HTA at the MS level, and whether it will positively affect local reimbursement timelines. If the evidence used in the JCA is not relevant for all MS (e.g., in some cases, ITCs are not accepted), MS would need to request additional evidence as part of MS level HTA , which may adversely affect reimbursement timelines.
- **For patients**, there is a risk of delayed access to innovative treatments, especially in MS where reimbursement is currently granted rapidly after market approval or where early-access mechanisms exist.

Conclusion and recommendations

- Our results show that many PICOs will be needed for products launching in an indication where treatment patterns are complex and vary across MS. These findings are in line with a total of 17 other PICO simulations conducted across oncology and rare disease space, where the median number of PICOs in the base case was 8 (range 5-18), and 17 for the worst-case scenarios (range 8-88).[3] It also reflects 3 PICO simulations published by EUnetHTA 21 which led to 5-9 PICOs after consolidation.[4-6]
- As MS and HTDs prepare for the EU JCA, key uncertainties remain such as a detailed description of the scoping process and how PICOs will be consolidated, a detailed dossier template, and methodology guidelines.
- Moreover, HTD input on the assessment scope remains limited. While the latest guidance allows for patients, clinical experts, and other experts to provide input into the draft PICO scope, HTD input will only be sought if deemed necessary by the JCA subgroup.[1]
- The current uncertainties and limited HTD input create the risk of MS PICO needs not being fully addressed. As the EU JCA evolves, we believe it is essential for HTDs to not only engage with the Joint Scientific Consultations (JSC) to anticipate PICO needs, but also have the opportunity to proactively propose PICOs for the assessment scope. Additionally, transparency about MS requesting specific PICOs is needed to facilitate prediction of PICOs for future products and thus ensure MS evidence requirements are fully met.
- Such improvements are key to achieving the objectives of the EU JCA: more efficient use of resources, and wider and faster availability of innovative products for patients throughout the EU. This would benefit MS, HTDs, healthcare providers, and most importantly, patients.

Abbreviations

- ATMP = Advanced technology medicinal product
- CHMP =Committee for Medicinal Products for Human Use
- DCR = Disease control rate
- DoR = Duration of response
- EMA = European medical agency
- ESMO = European Society for Medical Oncology
- EU = European Union
- HTA = Health technology assessment
- HTAR = Health technology assessment regulation
- HTD = Health technology developer
- IMP = Investigational medicinal product
- ITC = Indirect treatment comparison
- JCA = Joint clinical assessment
- JSC = Joint Scientific Consultations
- MS = Member state
- ORR = Objective response rate
- OS = Overall survival
- PFS = Progression free survival
- PICO = Population, intervention, comparator, outcome
- PRO = Patient reported outcome
- SmPC = Summary of product characteristics

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Disclosures

Despiegel N, Dirnberger F, Majer I, Takundwa R and Ubi S are employees of Amgen and hold Amgen stocks. Anastasaki E, Oswald C, Szawara P and van Engen A are employees of IQVIA, and van Engen A holds IQVIA stocks.

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