HTA97

Impact of Additive PICOs in a European Joint Health Technology Assessment: A Hypothetical Case Study in Lung Cancer

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Highlights

- In first line NSCLC, at least 10 PICOs would be predicted, exceeding EUnetHTA 21's prediction of a maximum of five
- There would be a minimum of 280 requested analyses. More realistically, it could be expected that there are between 560 and 840 analyses requested
- Ability to deliver a timely, high-quality submission and provide understanding of the feasibility of analysis requests would be enhanced with early, meaningful engagement with the health technology developer
- To ensure quality and timely delivery, appropriate resourcing will be required to assess each submission
- A further transparent, evidence-based approach to producing common European PICOs is required, focussed on populations and comparators, supplemented by complimentary analyses at a Member State level, particularly for safety outcomes

Introduction

The implementation of the EU HTA Regulation (HTAR) in 2025 will create a joint clinical assessment (JCA) for new medicines, starting with oncology and ATMPs. This will require the development of an assessment scope that "shall be inclusive and reflect Member States' needs in terms of parameters and of the information, data, analysis and other evidence to be submitted by the health technology developer" [1], particularly (a) the patient population; (b) the intervention(s) (c) the comparators and; (d) the health outcomes (known as the PICO).

In a proposal [2] developed under a service contract with the European Commission, the EUnetHTA 21 consortium envisages that a PICO process could be as follows:

1. Survey sent out to each Member State (MS) for their required PICOs, based on national policy questions
2. Consolidate MS PICOs by removing duplicates
3. If only one MS requested a PICO, discuss if it is needed
4. Combine all outcomes requested by MS and apply to all PICOs
5. PICOs are defined by a population. Where more than one specific comparator is requested, a new PICO is created for the additional comparator.

Objective

To estimate what an EU HTA set of PICOs and associated number of analyses that would be requested for a hypothetical new oncology medicine, product X, for the first-line treatment for non-actionable mutation metastatic non-small cell lung cancer (1L naNSCLC).

Methods

Using the IQVIA HTA Accelerator database, HTA reports on the latest medicine launched in 1L naNSCLC from HTA bodies in the EU were reviewed to assess the PICO of interest in each country. Based on the above information the likely consolidated PICOs for the JCA of product X were determined following the approach as laid out in the EUnetHTA 21 scoping proposal [2]. It was assumed that the clinical trial design for product X was similar to that of the latest assessed product (i.e., comparators and endpoints).

Clinical, quality of life and safety outcomes were included. Specific outcome measures (including instrument scales) were included when requested by a MS, assuming a single outcome measure assessed for each. For safety, nine key safety outcome categories were identified based on the PICO requests and the minimum safety outcomes outlined in EUnetHTA 21's draft endpoint consultation document [3].

Sensitivity analysis was undertaken to analyse the impact of additional PICO requests. In addition, the impact of additional subgroups and outcome measures on the total number of analyses was assessed. Lastly, additional safety endpoints based on IQWiG submission requirements were included, reflecting that the draft endpoint consultation document allows for this.

Country	Population	Comparator
	EMA label	Cisplatin in combination with vinorelbine, gemcitabine, docetaxel, paclitaxel or pemetrexed ***OR*** Bevacizumab in combination with platinum-based chemotherapy ***OR*** Nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy
	Trial ITT	Platinum doublet chemotherapy, namely combination of standard chemotherapy consisting of a platinum derivative (cisplatin or carboplatin) and a third-generation cytostatic
	PD-L1 ≥50%	Pembrolizumab monotherapy
	Squamous	Pembrolizumab in combination with carboplatin and (nab-)paclitaxel
	Non-squamous	Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin
	Squamous; PD-L1 <50%	Cisplatin in combination with a third-generation cytostatic ***OR*** Carboplatin in combination with a third-generation cytostatic ***OR*** Carboplatin in combination with nab-paclitaxel ***OR*** Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel ***OR*** Nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy
	Squamous; PD-L1 <1%	Carboplatin in combination with vinorelbine or gemcitabine or paclitaxel ***OR*** Nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy
	Squamous; PD-L1 ≥1%-<50%	Pembrolizumab in combination with carboplatin and a taxane
	Non-squamous; PD-L1 <50%	Pembrolizumab in combination with carboplatin and pemetrexed
	Non-squamous; PD-L1 <50%	Cisplatin in combination with a third-generation cytostatic ***OR*** Carboplatin in combination with a third-generation cytostatic ***OR*** Carboplatin in combination with nab-paclitaxel
	Squamous; PD-L1 ≥50%	Pembrolizumab monotherapy
	Non-squamous; PD-L1 <50%; adeno- or large-cell carcinoma	Pemetrexed in combination with a platinum drug (carboplatin or cisplatin)
	Non-squamous; PD-L1 <50%	Atezolizumab with bevacizumab, carboplatin and paclitaxel
	Non-squamous; PD-L1 ≥50%	Pembrolizumab monotherapy

Table 1: Relevant PICOs for hypothetical product X. Comparators in green font are assumed to be addressed by data in the clinical study report. Nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy has been added as a relevant comparator in addition to those previously requested in Member States where this treatment is reimbursed and has a positive HTA. PICOs 11-14 (blue shading) refer to the additional PICOs when the NICE scope was included in the analysis.

Results

At time of research, the European Medicines Agency (EMA) has approved 11 different medicines for 1L naNSCLC, aligned with current ESMO guidelines [4]. The latest approval in 1L naNSCLC was that of nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy versus platinum-based chemotherapy [5]. The trial included the LCSS and EQ-5D PRO instruments, with 9 and 6 scales, respectively, covering HRQoL, symptoms and health status.

Six out of 27 EU MS have published a HTA report on this indication to date [6-11]. Three HTA agencies (G-BA, Medicinrådet and ZIN) included a PICO in their report. For the remaining three (AOTMiT, HAS, AEMPS) the PICOs were derived from the observed populations, comparators and outcomes assessed in their HTA reports.

As a proxy for the other 21 Member States, we also looked at the published scope from NICE (England) and included this scope [12] in a sensitivity analysis. Although the UK is not in the EU, it could be reasonably expected that some EU Member States may refer to the NICE scope in determining their PICOs given that a scope is typically published prior to marketing authorisation informed by a deliberative process with patients, clinicians, and the manufacturer involvement.

The number of PICOs per country ranged from 1 to 4. Applying the EUnetHTA 21 scoping process results in 10 different PICOs for the JCA of product X (Table 1). For 5 out of the 10 PICOs head-to-head RCT data would be available. Inclusion of NICE increased the number of PICOs for the JCA to 14 (6 of which head-to-head evidence would be available). Six (excluding NICE) to eight (including NICE) out of these PICOs were requested by only one of the countries studied. Assuming Member States do not specify additional safety outcomes than those listed, a minimum of 28 outcomes would be needed per PICO in the base case (Figure 1). Applying these endpoints to all 10 PICOs would result in 280 requested analyses in total, assuming just one outcome measure per outcome and no subgroups per PICO.

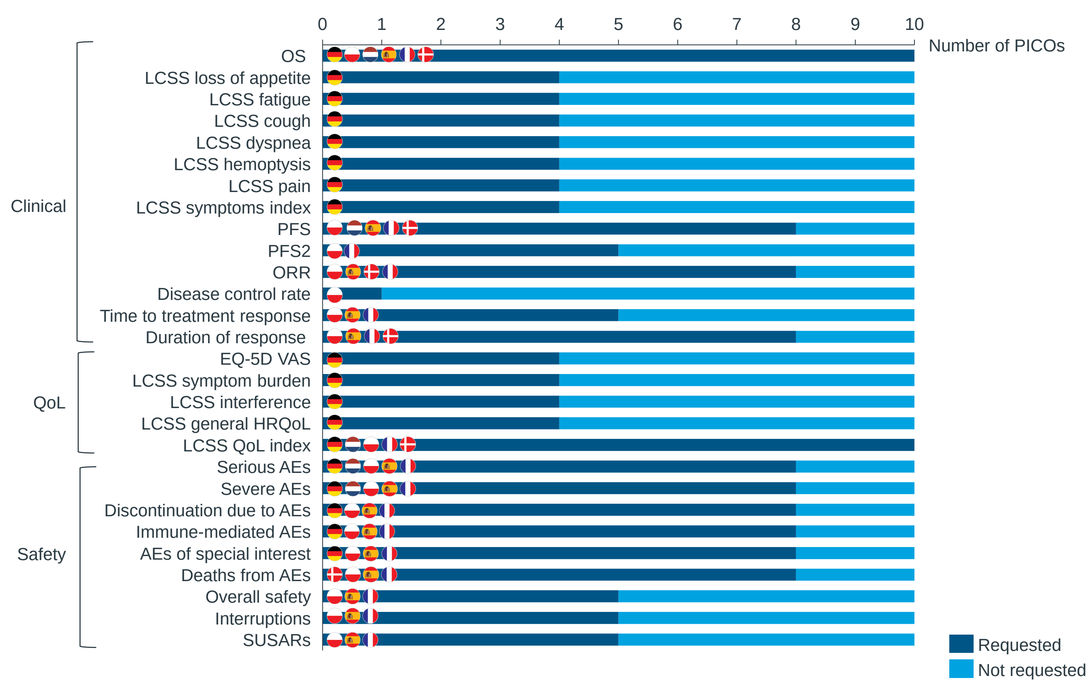

Figure 1: Relevant outcomes for hypothetical product X. The dark blue bars indicates PICOs for which at least one MS requested the specific outcome. The light blue bars indicates PICOs for which the outcome was not specifically requested by any of the Member States but for which the outcomes would need to be presented in the JCA according EUnetHTA 21's scoping process.

Sensitivity analyses showed that the number of requested analyses rapidly increased with each additional outcome measure (e.g., landmark analysis) per outcome (cumulative, 560 analyses) and subgroup per PICO (cumulative, 840 analyses). If Germany was to request additional safety endpoints as per their requirements, this would result in an additional 430 analyses alone across the 10 PICOs. The analytical complexity growths exponentially from 280 to 4,260 analyses across 10 PICOs when just one additional outcome measure per outcome, one subgroup and 43 additional safety endpoints are requested (Figure 2).

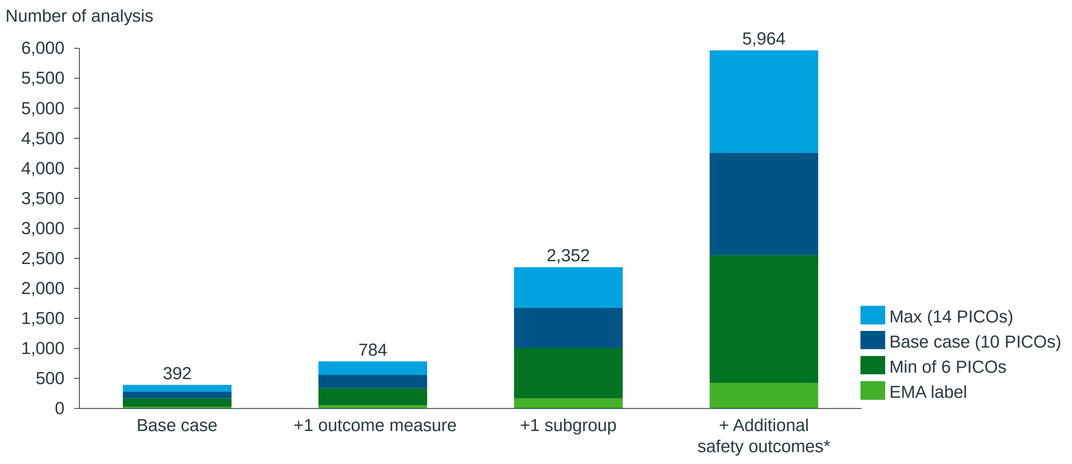

Figure 2: Impact of cumulative PICO related requests on total number of analyses requested. *Based on German IQWiG request for events of special interest, assuming no complementary safety analyses for Germany.

Discussion

EUnetHTA 21's final scoping proposal suggests most new medicines would have a small number of PICOs (maximum of five in complex cases). However, our analysis in a common oncology indication shows that the proposed process could lead to between 10 to 14 PICOs. Six to eight PICOs requested by only one MS could potentially be taken out in the consolidation phase, but these PICOs are clinically plausible, and it would be reasonably expected that at least one of the remaining 21 Member States would also request them. This estimate is also conservative; in addition to being based on only a small number of MS PICOs, the sub populations and comparators available now could reasonably be expected to increase by 2025.

Using conservative assumptions, there would be a minimum of 280 requested analyses. More realistically, it could be expected that there are between 560 and 840 analyses requested. The most significant number of analysis requests will be for safety analyses if Germany outlines their current requirements in the PICO survey (up to 5,964 in total across 14 PICOs). Given the unique requirements of Germany on safety, we recommend that these are handled at a MS level as complimentary analyses specific to their own PICOs and not applied across other PICOs where no MS would have requested them (70% of 430 safety analyses would be redundant).

Conclusions

The proposed additive PICO approach for some indications will lead to a significant number of PICOs, larger than EUnetHTA 21 has envisaged. Furthermore, unique needs of one MS for safety outcomes across all PICOs will lead to more analyses than would have been requested across Europe today, partly negating the aim of reduced duplication.

Based on EUnetHTA 21's proposal, it will be critical that sufficient resource is available for each JCA to undertake a high-quality assessment within the timeframe set out in the Regulation, ensuring Member States can use the JCA report without delaying time to patient access. Most importantly, further alignment and harmonisation of a European focussed PICOs, particularly regarding populations and comparators, based on a transparent and evidence-based methodology, is required, with engagement across all stakeholders.

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