Initiate. WITH PURPOSE

PICO consolidation in European HTA scoping: Examining PICO variations in oncology drugs in the context of the European Joint Clinical Assessment

Daniel Hollard [1], Georgia Roberts [1], Imogen Taylor [1], Jonathan Gibson [1], Oliver Darlington [1]

1. Initiate Consultancy, London, UK.
Study sponsored by Initiate Consultancy

SUMMARY

OBJECTIVES

- Considering the forthcoming EU HTA regulation, this study sought to investigate the disparities in Population, Intervention, Comparator, and Outcome (PICO) criteria across HTA assessments for oncology drugs in Europe and England, and to analyse these variations in anticipation of potential implications for data requests for HTDs, so that they can tailor their evidence generation strategies.

METHODS

- A targeted review examined 45 HTA reports for five oncology drugs, drawing from publicly available documentation from five national HTA bodies:
  - NICE (England)
  - HAS (France)
  - G-BA (Germany)
  - NCPE (Ireland)
  - ZIN (Netherlands)
- PICO information was extracted to identify variations among these countries.

FINDINGS

- The study revealed numerous disparities in PICO questions in Europe and the UK.
- Treatment line and comparators played a big role in these differences.
- Two drugs, Enhertu® and Tecentriq®, had the most variations in PICO questions.
- No drug had a consistent PICO across all five countries.

RECOMMENDATIONS

- HTDs will need to prepare for a varied data request and be willing to compile a dossier with covering a range of different PICOs.
- HTDs can benefit from engagement with the JSC to tailor their evidence-generation plan to suit these varying PICOs.

BACKGROUND & AIMS

- The European Union's (EU) Health Technology Assessment (HTA) Regulation 2021/2282, which will come into full effect for oncology drugs and advanced therapeutic medicinal products (ATMPs) in January 2025, aims to streamline drug access for patients through a standardised Joint Clinical Assessment (JCA) process.
- A crucial aspect of this initiative is harmonising the Population, Intervention, Comparator, and Outcome (PICO) questions across EU member states. Unlike in localised HTAs, the new European HTA framework needs to address policy questions relevant to the widely differing healthcare systems in which these assessments will be used.
- This challenge arises from the significant disparities in practices, guidelines, policies, treatment availability, and even the epidemiological landscape across these countries.
- This study aims to investigate the extent of variations in PICO criteria specifically within the context of HTA assessments for oncology drugs in England, France, Germany, Ireland, and the Netherlands.

METHODS

- This study investigated variations in PICO criteria for oncology drugs across four European healthcare systems and England. A targeted review analysed 45 Health Technology Assessment (HTA) reports from esteemed national HTA bodies:
  - England: National Institute for Health and Care Excellence (NICE) [1]
  - France: French National Authority for Health/Haute Autorité de Santé (HAS) [2]
  - Germany: Federal Joint Committee/Gemeinsame Bundesausschuss (G-BA) [3]
  - Ireland: National Centre for Pharmacoeconomics (NCPE) [4]
  - Netherlands: National Health Care Institute/Zorginstituut Nederland (ZIN) [5]
- The searches were performed between December 2023 and January 2024, and looked at any reimbursement decisions which took place in 2019 or later.

- Data was collected on the PICO questions assessed by each HTA body for nine products. However, not all drugs were assessed within the same indication in each jurisdiction. As such, only the five products with data available for all five jurisdictions are presented here.
- Publicly accessible data from these reports, specifically the PICO questions, were extracted and analysed to identify potential 'unique PICO combinations', defined as the amount of potential variations to the PICO that could result from country-to-country divergence. These combinations were calculated using the combinations formula ($n! \frac{n!}{r!(n-r)!}$).

RESULTS

- The analysis demonstrated substantial disparities in PICO questions for several oncology drugs. Please refer to Table 1 for the PICO questions assessed for each drug, colour-coded to illustrate the extent of variations.
- Treatment line and relevant comparators emerged as the primary drivers of these differences, impacting five treatments each.
- Among the drugs assessed, two stood out for having the highest number of unique PICO combinations, with eight potential combinations each:
  - Enhertu® for HER2-positive unresectable or metastatic breast cancer after one or more anti-HER2 treatments
  - Tecentriq® for adult patients with NSCLC with a high risk of recurrence, presenting with PD-L1 tumour expression ≥ 50% on tumour cells and not presenting with EGFR-mutated or ALK-gene rearranged (ALK-positive) NSCLC
- The review highlights significant disparities in PICO criteria across European jurisdictions for oncology drugs. These variations underscore the challenge of adopting a pan-European approach to health technology assessment, particularly regarding Comparator and Treatment Line. Notably, none of the drugs had consistent PICO questions across all jurisdictions.
- One limitation of this study is its failure to consider jurisdictions beyond the included countries. Ideally, the analysis would have encompassed data from countries with greater epidemiological or socioeconomic diversity. However, due to differing reporting standards among these countries, this was not feasible.
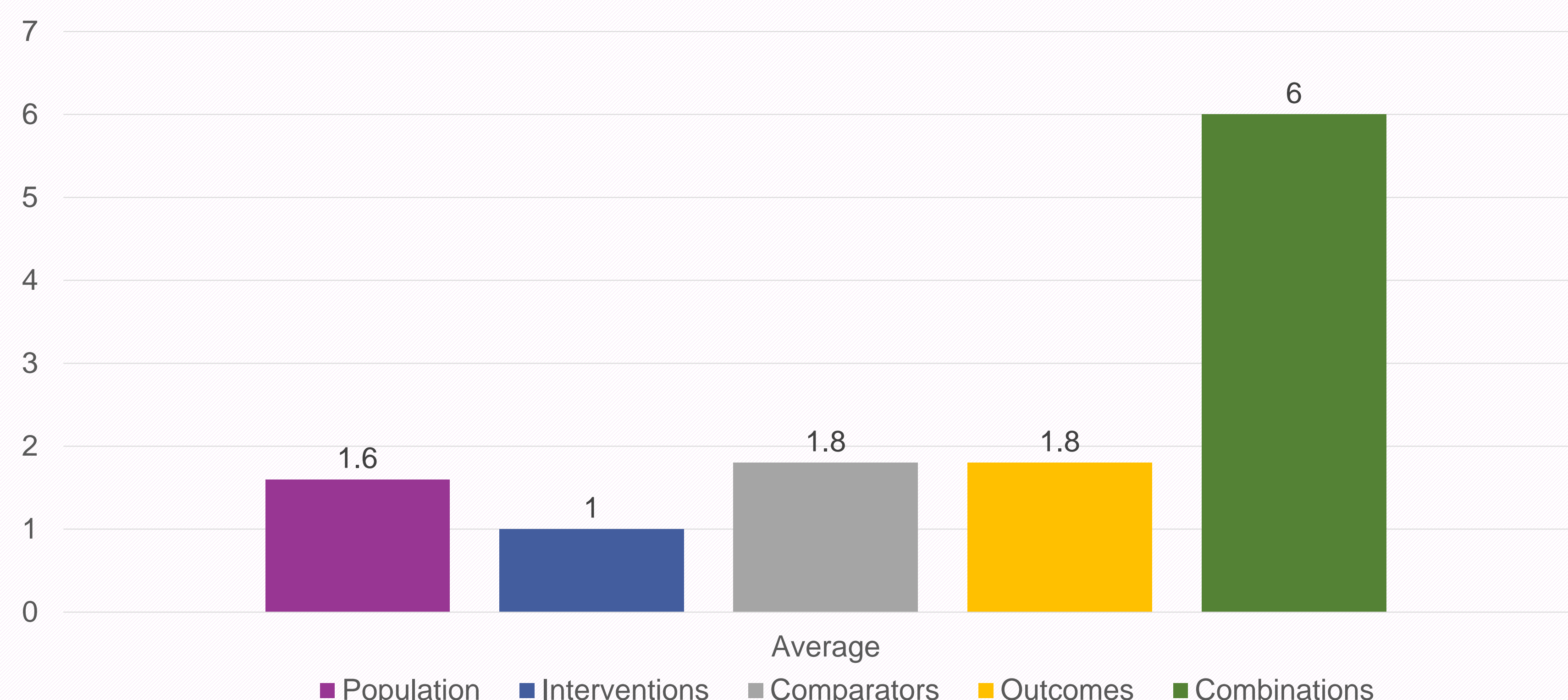
Table 1. Variations in PICO criteria across oncology products in five different countries

Interventions	Population and treatment line		Comparators	Primary outcome	No. of combinations
Lynparza® (olaparib) with bevacizumab	Adults with advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer in response (complete/partial) following platinum-based chemotherapy (in combination with bevacizumab), whose cancer is associated with homologous recombination deficiency positive status	1st line maintenance OR 2nd line	Bevacizumab and platinum-based chemotherapy OR active monitoring	Progression-free survival	4
Enhertu® (trastuzumab deruxtecan)	HER2-positive unresectable or metastatic breast cancer who received: trastuzumab and a taxane/≥1 or ≥2 prior antiHER2-based regimens	2nd line OR 3rd line	Trastuzumab emtansine OR standard of care	Progression-free survival OR overall survival	8
Venclyxto® (venetoclax)	Patients with CLL mutation for whom a B-cell receptor pathway inhibitor is unsuitable/whose disease has progressed after treatment with chemoimmunotherapy/B-cell receptor pathway inhibitor	1st line OR 2nd line OR 3rd line	Bendamustine and rituximab	Overall survival OR progression-free survival	6
Darzalex® (daratumumab) in combination with LEN and DEX	Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant	1st line	LEN and DEX OR daratumumab in combination with bortezomib, melphalan, and prednisone	Overall survival OR progression-free survival	4
Tecentriq® (atezolizumab)	Adult patients with NSCLC with a high risk of recurrence, presenting with PD-L1 tumour expression ≥ 50% on tumour cells and not presenting with EGFR-mutated or ALK-gene rearranged (ALK-positive) NSCLC	1st line OR 1st line (adjuvant treatment)	Pembrolizumab as monotherapy/in combination with chemotherapy OR best supportive care	Overall survival OR disease-free survival	8

Key:
- Substantial differences in PICO
- Some differences in PICO
- Minimal differences in PICO
- No differences in PICO

Abbreviations: Anaplastic Lymphoma Kinase; ALK, Chronic Lymphocytic Leukaemia; CLL, Dexamethasone; Dex, Epidermal Growth Factor Receptor; EGFR, Human Epidermal Growth Factor Receptor 2; HER2, Non-Small Cell Lung Cancer; LEN; Lenalidomide, NSCLC, Programmed Death Ligand 1; PD-L1.

Figure 1. Average number of variations in each PICO measure for the five oncology drugs investigated

	Average
Population	1.6
Interventions	1
Comparators	1.8
Outcomes	1.8
Combinations	6

CONCLUSIONS

- The observed variations in PICO criteria across these national HTAs highlight the challenges of achieving a unified approach during the JCA scoping phase. While this analysis focused on five nations, the inclusion of additional member states is likely to further increase the number of PICOs identified.
- To effectively navigate this complexity as national frameworks converge, a comprehensive evaluation of both clinical and contextual data is necessary. Recognising these variations is crucial for tailoring evidence-generation strategies to optimise health technology assessment outcomes across different jurisdictions. To this end, close collaboration between HTA bodies and early engagement with the Joint Scientific Consultation (JSC) is essential for strategically navigating the JCA scoping process.

References

1. NICE website: https://www.nice.org.uk/
2. HAS website: https://www.g-ba.de/english/
3. GBA website: https://www.g-ba.de
4. NCPE website: https://www.ncpe.ie/
5. ZIN website: https://www.inahta.org/members/zinl/