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Predicting PICOs for EU Joint Clinical Assessment: Lessons from PICOs in Relative Effectiveness Assessments (REA) from EunetHTA Joint Action 3 Project

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INTRODUCTION

The objective of EUnetHTA Joint Action 3 (JA3) (2016-2021) was to define and implement a sustainable model for the scientific and technical cooperation on Health Technology Assessment (HTA) in Europe[1]. One of the tasks was to produce joint health technology assessments[2]. EUnetHTA JA3 ultimately produced "Relative Effectiveness Assessments" (REA) for 20 medicines[3].

OBJECTIVES

The objectives of this research were to identify the PICOs determined by EUnetHTA reviewers for medicines during the JA3 project (2016-2021), to anticipate how PICO selection might be done for the forthcoming EU Joint Clinical Assessment.

MATERIALS & METHODS

The EUnetHTA REA exercise assessed 20 medicines. All REAs conducted under JA3 were eligible for inclusion in this study. One assessment (satralizumab) was discontinued due to changes in the EMA timelines, another (enasidenib) because the product was withdrawn from Marketing Authorization. Four products were COVID-19 treatments.

REAs which were discontinued were excluded as were assessments for COVID-19 treatments (Table 1). We extracted the information on assessors/stakeholders input and PICOs. Descriptive statistics were computed for each category.

RESULTS

The 14 REAs (Table 1) were authored by 9 countries (Austria, Croatia, Finland, France, Germany, Netherlands, Norway, Portugal and Sweden) and co-authored by 11 countries among which were, in addition, Ireland, Poland, Slovakia and Spain.

Table 1 List of selected REAs

PTJA 01 Midostaurin	PTJA 06 Polatuzumab vedotin	PTJA 10 Crizanlizumab	PTJA 16 Venetoclax
PTJA 02 Regorafenib	PTJA 07 Ustekinumab	PTJA 11 Cefiderocol	PTJA 17 Elivaldogene autoemcel (Eli-Cel)
PTJA 03 Alectinib	PTJA 08 Siponimod	PTJA 12 Glasdegib	
PTJA 04 Sotagliflozin	PTJA 09 Brolucizumab	PTJA 14 Pretomanid	

Stakeholder inputs (HCPs and patient representatives) were sought for these REAs but 2 REAs received no patient input, and HCPs were not involved in 3 REAs, one due to conflict of interest.
Six products were Oncology drugs: alectinib, glasdegib, midostaurin, polatuzumab, regorafenib and venetoclax.

Patient populations

Most medicines were assessed based on the population stated in their proposed EMA label. Two medicines had 2 sets of populations in their REA report: polatuzumab (for the treatment of diffuse large B-cell lymphoma) and ustekinumab (for the treatment of ulcerative colitis). The authors of the reports were different, as were the therapeutic areas. The analysis of these populations is presented in another poster.[4]

Comparators

The existing comparators (on average, 4 comparators per product) were chosen from EU clinical guidelines. It seems that the assessors opted for the largest possible set of comparators, with the majority of REAs focusing on 2 or more comparators (mean=4), up to a maximum of 11 comparators selected for pretomanid (Dovprela - an antibiotic for the treatment of multi-drug-resistant tuberculosis)

OUTCOMES

The Outcomes lists were of different structures and lengths (average of 8 for efficacy, average of 7 for safety) some differentiating "critical outcomes" from "other outcomes", some others not.

HRQoL requirement was a standard, sometimes mentioned in the "critical" outcomes.

Only three of the efficacy outcomes were common for all Oncology drugs (OS, PFS, Response Rate) which ranged from 3 to 9 across the 6 REAs analyzed.

Safety outcomes were expressed very differently from one REA to another, some using the AE grade classification, others not.

Table 2 Number of PICOs for the 14 drugs selected in JA3

Sample = 14 | Population | Comparators | Outcomes

			Efficacy	Safety
Min-Max	1-2	1-11	3-13	3-14
Mean		4	8	7
Median		5	7	7

Table 3 Number of PICOs for the 6 oncology drugs in JA3

Sample = 6 | Population | Comparators | Outcomes

			Efficacy	Safety
Min-Max	1-2	2-5	3-9	6-14
Mean		3	6	8
Median		4	6	8

Efficacy outcomes were not always prioritized. As clinical trials are not designed/powered to evaluate as many outcomes, building such long lists seems more of a theoretical exercise. Also, given no head-to-head trials will be available for many of the comparisons selected in PICOs, it seems predictable that it will be very difficult to get results on many of these outcomes as part of indirect comparisons.

Safety outcomes were not standardized. However, looking at the "PICOs exercise" done by EUnetHTA 21 in 2023[5], we can observe a better standardization of the safety outcomes. They still produced comprehensive and wide lists of comparators and outcomes with no prioritization.

CONCLUSIONS

In this analysis, we see that the PICOs reviewed for the 14 medicines selected from the JA3 EUnetHTA project were very different in their presentations and content/wording, even for drugs in the same therapeutic area (e.g. Oncology).

A minority of drugs were assessed for 2 different patient populations.

The comparators and outcomes lists were very comprehensive and wide.

The EU JCA coordinators should consider improving standardization in the wording of PICOs, and consider a prioritization in their comprehensive lists of Comparators and Outcomes. This would make the difference between comprehensiveness and reality, to avoid PICOs becoming a list of impossibilities.

REFERENCES

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