PT19

Can Estimands Support Aligned Evidence Generation for EU HTA?

Reflections on their role in JCA, PICO Alignment and Beyond

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Objectives

- To examine how the ICH E9(R1) estimand framework is reflected in EU HTA processes, particularly in Joint Clinical Assessments (JCAs), and to evaluate alignment between estimand attributes and the PICO framework.
- To identify whether a shared language is emerging between regulatory and HTA evidence requirements.

Introduction and Background

- The ICH E9(R1) Addendum introduced the estimand framework to define treatment effects through five attributes: population, treatment conditions, variable, intercurrent event strategy, and summary measure.
- In contrast, the EU HTA Regulation (2021/2282) established JCAs based on policy-driven PICOs.
- We explore how current EU HTA guidance incorporates estimand principles and how PICO elements map onto estimand attributes to improve alignment.

Materials and Methods

- A structured review was conducted of EU HTACG JCA methodological guidance documents and selected templates for the process
- Each document was examined to identify explicit or implicit references to estimand concepts, including the five core attributes.
- Besides the JCA, case examples (Wegovy, Mounjaro, Skyrizi) were reviewed from EMA and HTA agency reports (NICE, HAS, ZIN, G-BA) to explore differences in the Regulatory and HTA perspectives on estimands.

Results

Summary of HTACG Guidance

Across the 2024 HTACG methodological series, the role of **estimands** is emerging, though unevenly articulated across documents.

1) The **Scoping Guidance** defines PICOs as *policy-driven comparative effectiveness questions*, derived from Member State input. It contrasts these with **estimands**, which are *scientific constructs* defined in clinical trial protocols, and explicitly notes conflicts between **Statistical Analysis Plans (SAPs)** and PICO-driven requirements when evidence is reanalysed for JCAs.

2) The **Validity of Clinical Studies Guidance** links *external validity* to the fit between the study estimand and the JCA PICO—positioning this alignment as essential to evidence relevance for HTA.

3) The **Outcomes Guidance** highlights overlap between the PICO *Outcome* element and the estimand attribute *variable (endpoint)* but recognises that the two frameworks differ in terminology and objectives.

4) The **Multiplicity and Subgroup Analysis Guidance** requires clear reporting of estimands and tested hypotheses, particularly for post-hoc analyses performed to match national PICO needs.

5) The **Evidence Synthesis Guidance** mandates that analyses answer PICO-formulated questions but still omits explicit guidance on *intercurrent events* and *summary measures*—the two estimand attributes with no PICO equivalent.

Results (cont.)

JCA Template and Process Guidance

1) The **Guidance on Filling in the JCA Dossier Template (HTACG, 2024)** provides detailed technical specifications for structuring evidence and results **by PICO**, ensuring comparability across submissions.

2) Templates standardise tables for reporting results, certainty assessments, and multiplicity control, yet remain **entirely PICO-based**, with no fields referencing **estimands**—even in sections describing study objectives or analysis populations.

3) Similarly, the **Joint Scientific Consultation (JSC)** templates, intended to align early regulatory and HTA advice, require detailed **PICO specifications** but lack corresponding estimand descriptors.

4) This omission highlights a persistent disconnect: while JCAs demand clarity on *what* to compare (the PICO), they provide no structured mechanism to specify *how* the comparison is estimated (the estimand).

Case studies: Regulatory vs HTA Perspectives on Estimands

Product	Regulatory Perspective	HTA Perspective
Wegovy (semaglutide)	EMA EPAR defines estimands based on % weight loss and mean % change, with intercurrent events handled via sensitivity analyses.	HAS (France) and ZIN (Netherlands) questioned long-term effectiveness and adherence; assessments adopt a *treatment-policy* view reflecting real-world discontinuation.
Mounjaro (tirzepatide)	EMA and MHRA reports specify distinct estimands ("efficacy" vs "treatment-regimen") for weight endpoints.	NICE TA1026 evaluates effectiveness under routine conditions, considering adherence and eligibility limits — a *real-use* estimand distinct from trial efficacy.
Skyrizi (risankizumab)	CHMP variation report defines estimands aligned with protocol-specified intercurrent event handling.	HTA (e.g. NICE, G-BA) focuses on population heterogeneity and switching patterns, implying a broader *policy-relevant* estimand.

Discussion and Conclusions

- Estimand concepts are increasingly recognised in EU HTA guidance but remain only partially integrated.
- Alignment exists for population, intervention, comparator, and outcome, but *intercurrent events* and *summary measures* remain unaddressed.
- Integrating all five estimand attributes into HTA frameworks and JCA templates would ensure that *what* is compared (PICO) and *how* it is compared (estimand) are defined consistently, improving coherence and credibility across regulatory and HTA evidence.

References

1 ICH E9(R1) *Addendum on Estimands and Sensitivity Analysis in Clinical Trials* (EMA/CHMP/ICH/436221/2017).
2 EU Regulation 2021/2282 on Health Technology Assessment (HTAR).
3 HTACG (2024): *Scoping Process for JCAs; Validity of Clinical Studies; Outcomes; Multiplicity & Subgroup Analyses; Evidence Synthesis; JCA Dossier Template – Medicinal Products.*
4 EMA EPARs: *Wegovy (semaglutide), Mounjaro (tirzepatide), Skyrizi (risankizumab).*
5 HTA decisions: NICE TA1026 (2024); HAS (2022); ZIN (2023); NCPE (2023); G-BA (2023).
6 Remiro-Azócar A et al. *Some considerations on target estimands for HTA. Pharm Stat* 2023.
7 IQWiG & Regulators. *Joint HTAb–Regulatory Perspectives on Understanding Evidence Challenges,* 2023.

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