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Setting **EU HTA** Priorities

Insightful PICOs. Precision Methods.
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Too much to do?

The EU HTA Joint Clinical Assessment (JCA) aims to streamline the evaluation of health technologies across EU member states. A critical component of this process is the identification of relevant PICO research questions—Population, Intervention, Comparator, and Outcomes—for each assessment.

Member states are expected to request a large number of analyses across multiple PICOs, which could significantly impact health technology developers. This demand will require careful planning, especially around resource allocation and workload management. Over- or under-investing in analytical resources could compromise the efficiency and effectiveness of the JCA process, increasing the risk of delays to market access.

Given this, a central question emerges:

How can we strategically prioritise PICO analyses to ensure that resources are used effectively and timelines are maintained?

How valid are the PICOs?

PICOs cannot be evaluated without supporting data. Where such data exist, internal statistical validity becomes critical for determining which analyses are worth pursuing.

Randomised, double-blind controlled trials (RCTs) offer the highest level of internal validity. Randomisation helps ensure that prognostic factors and treatment effect modifiers are evenly distributed between treatment arms. Blinding, combined with the controlled environment, helps maintain objectivity during outcome measurement.

Considering this methodological strength, PICOs based on RCTs should be accepted by developers and prioritised accordingly.

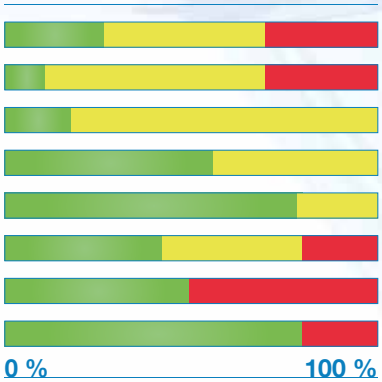
In contrast, PICOs relying on non-randomised data—such as those involving indirect comparisons—typically present lower levels of internal validity.

This raises key strategic questions:

Should these comparisons be included? And if so, how should developers prioritise among a potentially long list of such requests?

Dealing with bias

The internal validity of non-randomised PICOs largely depends on the extent of selection bias, confounding, the clarity and timing of endpoint definitions, and the quality of statistical adjustments used to mitigate these issues.



PICOs based on published aggregate data tend to have lower internal validity due to limited capacity to adjust for confounding. By contrast, PICOs derived from individual patient data (IPD)—especially when analysed using frameworks like target trial emulation—can achieve higher internal validity, assuming appropriate statistical methods are applied correctly.

Thus, the validity of non-randomised PICOs should be seen as a continuum, rather than a binary classification. The presence and impact of bias will vary; some biases can be mitigated, others cannot—often due to data limitations. Therefore, these PICOs should be assessed on a sliding scale of validity, shaped by both the nature of the data and the methods used to analyse them.

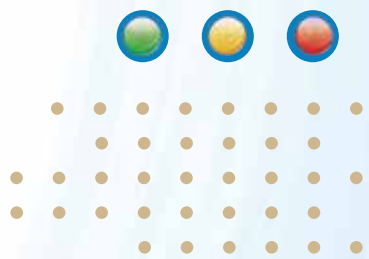
Can we prioritise?

Prioritising PICOs should not be a subjective process that favours one stakeholder over another, nor should it disregard the needs of individual member states. An effective solution should aim to be objective, transparent, and defensible.

The key challenge lies in managing a high volume of PICOs without compromising interpretability, timeliness, or resource feasibility.

One suggested approach is to prioritise PICOs with higher internal validity and exclude those where it is extremely low. High internal validity is characterised by a reduction in both the type and extent of bias affecting the treatment comparison. For example, if selection bias can be addressed using propensity score matching, this increases the validity of the analysis.

Conversely, where there is extremely low internal validity—for instance, when baseline characteristics between treatment arms show little or no overlap—there may be a reasonable argument for excluding such comparisons from analysis.



Case-by case

The EU HTA Coordination Group's Guidance on the Validity of Clinical Trials encourages assessors to quantify risk of bias (RoB) as a proxy for internal validity. Similarly, the Methodological Guideline for Quantitative Evidence Synthesis underscores that comparisons based on RCTs with low RoB should be prioritised.

However, a practical challenge remains: PICOs must first be analysed by developers before assessors can evaluate their validity. The RoB framework used in the JCA process supports transparent and systematic prioritisation, but it may oversimplify complex scenarios, particularly those involving sophisticated adjustments. Consequently, **the level of internal validity required to support a PICO analysis is often context-specific, necessitating case-by-case judgment.**

Does low validity result in low priority?

A key challenge in prioritisation is that PICOs with low internal validity often demand significantly more resources to analyse properly, yet may not deliver proportionate value in terms of compelling evidence.

While analyses of such PICOs may be necessary for specific member states, the resources required could outweigh the benefit. Therefore, prioritisation must involve a strategic trade-off: is the investment in time and effort justified by the likelihood of generating robust, actionable evidence?

Statisticians are critical to this process. Their expertise allows them to weigh the analytical effort against the potential evidentiary value, ensuring that resources are directed toward comparisons that are most likely to influence decision-making.

Plan the strategy

Check out the recommendation on the back...

Martin Scott, Scientific Director

Recommendation

Owing to constraints on time and resources during the JCA process, prioritisation becomes not just a methodological concern, but a strategic imperative. By focusing on PICOs that are capable of delivering robust, timely, and credible results, developers can improve both the efficiency and the impact of the JCA submission.

PICO
based on RCTs

Accepted. Prioritised.

PICO
non-randomised

Assessed on a sliding scale of validity

PICO
timeline & resources

More input ≠ more insight. Big effort, small return on evidence?

With statistical support, internal validity is secured before peer review.

Internal Validity of Different PICOs and their Risk Profile

PICO 1	
Type of bias	**Risk**
Selection bias	→
Confounding	↑
Immortal time bias	→
Assessment bias	↓
Attrition bias	↓
Intercurrent event bias	↓
Trial bias	↓

PICO 2	
Type of bias	**Risk**
Selection bias	↑
Confounding	↑
Immortal time bias	→
Assessment bias	↑
Attrition bias	→
Intercurrent event bias	↓
Trial bias	→

PICO 3	
Type of bias	**Risk**
Selection bias	↑
Confounding	↑
Immortal time bias	↑
Assessment bias	↑
Attrition bias	→
Intercurrent event bias	↑
Trial bias	↑

↑ = No bias → = Bias adjustment possible ↓ = Bias adjustment not possible

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