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EU-HTA PICO SCOPING

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Introduction

The EU HTA Joint Clinical Assessment (JCA) process aims to streamline the evaluation of health technologies across EU member states. A critical part of this process is determining the number of "PICO" research questions (Population, Intervention, Comparator, and Outcomes) to be considered in each assessment.

Unsurprisingly, some stakeholders argue that a limited number of PICOs would simplify and harmonise assessments, making them more manageable and less costly for all parties involved. As a result, proposals have been made to reduce the number of PICOs sent to the health technology developer (HTD) for analysis. However, many of these initiatives rely on subjective criteria, e.g. including only PICOs that have requested by at least two member states.

Objective Criteria

Clearly, the decision to reduce the number of PICOs cannot be subjective, favouring one stakeholder over another. Nor can it be a decision that conspicuously disregards the needs of individual member states.

Since the primary concern with having too many PICOs lies in the challenges it poses for methodological execution, interpretability, as well as the time and resources needed for thorough analysis, **solutions aimed at reducing the number of PICOs should strive to be as objective as possible.**

Statistical Validity

Clearly PICOs cannot be evaluated if there are no data to support them. And yet, the harder one searches, the more likely it is that data will be found. **But, how "good" are these data for making informed decisions?**

This question should be answered by the concept of statistical validity, or more precisely, internal statistical validity. This is not a new concept. In fact, it is accepted that randomised controlled, double-blind trials have the highest degree of internal validity. This is because randomisation ensures that all prognostic factors and treatment effect modifiers are - on average - equally distributed between the study treatment arms. Furthermore, the controlled 'experimental' nature of the trial, coupled with blinding, ensures the objectivity of the post-randomisation observation period during which the clinical outcomes are captured and assessed.

Due to their high level of internal validity, PICOs that are entirely based on comparisons within RCTs should be readily accepted and analysed by health technology developers. We can refer to these as RCT PICOs. On the other hand, PICOs that are forced to rely on non-randomised data for the comparator in question, will, by definition, have lower levels of internal validity. We can refer to these as real-world data (RWD) PICOs, to reflect that the data orginated from outside an RCT.

Types of Bias

The level of internal validity of RWD-PICOs will be determined primarily by the degree of selection bias, confounding, and objective definition and scheduling of the clinical endpoints, as well as the ability of the statistician to 'deal' with these issues through adjustment methods. Clearly, RWD arising from publications in the form of aggregated summary results will - due to the inability to adequately adjust for much of the above - represent RWD-PICOs with lower levels of validity. Conversely, RWD-PICOs based on sources of individual patient data collected from a real-world database using a target trial emulation framework, for which methods of adjustment can be implemented, should be considered as having higher levels of validity, provided that the most appropriate methods are used and correctly implemented.

Consequently, the internal validity of RWD-PICOs will not be the same for all within this category and and will depend on the extent of the biases previously mentioned. Some biases will be present, some not. Some will be adjustable using statistical methods, others – e.g. due to the lack of data, will not. Subsequently, PICOs will constitute a sliding scale from higher levels to lower levels of validity, depending on the type and extent of bias present.

Drawing the Line

Despite the arguments already outlined, the question remains as to where the line should be drawn with regard to reducing the number of PICOs for assessment. Clearly, PICOs of high validity should be assessed; those of extreme low validity should not.

Higher levels of internal validity are determined by a reduction in the type and amount of bias affecting the treatment comparison. For example, **if selection bias can be adequately addressed, e.g. through propensity score matching, then this should be seen as a positive step towards increasing internal validity.** Similarly, if it can be shown that all possible confounders have been identified and used to adjust the analyses, then this should also be viewed favourably. Likewise, if the problem of not being able to adjust for unmeasured confounders has been addressed through methods such as quantitative bias assessment, then this should also be seen as a positive step in increasing the validity of the comparison.

On the other hand, if, for instance, the populations in each treatment arm differ substantially, such that there is little or no overlap in their baseline distributions, then the level of internal validity will be reduced. Similarly, if the study designs, including the definitions of the endpoints, are substantially different between the treatment arms to the extent that re-mapping will not be able to make them consistent, then the level of internal validity will also be reduced.

How Much is Enough?

The question of how much internal validity is required to support **the analysis of a PICO remains subjective in the sense that the decision should be made on a case-by-case basis.** The Guidance on the Validity of Clinical Trials written by the EU HTA Coordination Group goes some way into addressing this by requesting an assessment of the risk of bias (RoB) - akin to internal validity. The Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons also stresses the need to assess the RoB, as well as making the point that comparisons based on RCTs with low RoB should always be favoured.

The issue here is that **we have a case of closing the barn door after the horse has bolted** in the sense that the PICOs have already been requested and analysed by the time the assessor gets to review them. That is to say, the work has already been done. Nonetheless, the thinking behind the RoB assessment for the JCA does provide a framework for a constructive and objective process in determining which PICOs should be analysed, and which not. Contrary to the guidance however, when determining which PICOs to analyse, **an RoB or internal validity assessment should not categorise a treatment comparison as having low or high validity soley on the basis of weaknesses in the study design, but should acknowledge the statistical methods used to each of the biases in question**. After all, EU member states have requested analyses for PICOs to support national healthcare decisions, so every effort should be made to provide them.

Note, despite the focus on internal validity, neither the need for external validity, i.e. how representative the trial patients are of the indicated population, nor the need for precision is ignored. The case for precision is self-explanatory. The case for external validity, however, although undisputed as a requirement, remains an issue for all RCTs that are considered to have enrolled an unrepresentative sample of the population. This is, therefore, a wider issue for discussion and not something that can be resolved at the time of PICO development.

Check out the summary on the back...

Martin Scott, Scientific Director

Let's talk

Summary

Under the EU-HTA implementation act on joint clinical assessment, the responsibility for determining the list of PICOs rests with national payers, who will ultimately seek the advice of clinical experts and patients. Thereafter, when deciding if a particular PICO should formally undergo analysis, the process should strive to be as objective as possible. Ideally, this decision would rely on principles of statistical validity and an assessment of potential bias.

In this field, characterised by significant uncertainty, the determination of whether a PICO can be reliably analysed and interpreted falls within the purview of statistical expertise. **The central question is: will the available evidence be robust enough to support reliable judgments on treatment causality, and can it form the basis for sound decision-making?** In this regard, it is comparable to the regulatory requirements of Good Clinical Practice (GCP), which mandate the involvement of qualified personnel with statistical expertise in clinical study design.

Since the statistician has the deepest understanding of the data's availability and quality for a given indication, it is logical for them to evaluate the internal validity of the treatment comparison in question, as well as any necessary adjustments to mitigate potential biases. Therefore, given their pivotal role in ensuring that the results are robust and meaningful for healthcare decision-makers like payers and policymakers, **the statistician should take the lead in selecting the final set of PICOs to be analysed and included in the JCA dossier.**

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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