Early Systematic PICO Scenario Identification and Prioritization for EU HTA Joint Clinical Assessments

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Background and Objective

- The EU HTA Joint Clinical Assessment (JCA) dossier implies that Health Technology Developers (HTD) systematically identify and prioritize PICO (**P**opulation, **I**ntervention, **C**omparator, **O**utcome) scenarios before submission. The 60- or 100-day timeline after receiving the final scope is challenging, as submissions demand multiple distinct PICOs with robust evidence and indirect comparisons from all EU member states (MS.)
- PICO consolidation complexity stems from:
  - Heterogeneous MS requirements: Varying population definitions, national comparators, and healthcare-specific outcomes
  - Evidence generation demands: Each PICO requires comprehensive clinical evidence, literature reviews, and indirect treatment comparisons
  - Resource constraints: Addressing multiple PICOs simultaneously while maintaining methodological rigor
  - Process management: Coordinating simultaneous JCA submissions with EMA marketing authorization processes
- We present an AI-powered framework (PICO Radar™) that streamlines and prioritizes PICO development before JCA scoping by automating literature review tasks to efficiently synthesize the evidence
- This study aimed
  - to assess the feasibility of systematically identifying and prioritizing PICO scenarios for a hypothetical new dual GIP/GLP-1 agonist in insulin-dependent type 2 diabetes (IDT2DM) patients and
  - to validate this PICO generation method with an available example in advanced hepatocellular carcinoma (aHCC)

Methods

A five-step methodology was implemented (Figure 1)

1. Therapeutic Context Definition (indication analysis and disease characterization, current treatment pathway mapping and standard-of-care identification, focus on IDT2DM patients only)
2. Systematic Evidence Identification using bibliographic database searches (PubMed, Embase), Clinical trial registries (ClinicalTrials.gov, EudraCT), Guideline repositories and HTA agency databases, and applying predefined in-/exclusion criteria
3. Data Extraction and Quality Assessment: Application of standardized extraction forms for PICOs, quality assessment of extracted data by second review
4. PICO Matrix Development: Frequency analysis of identified PICO elements, probability calculations for scenario likelihood, statistical weighting algorithms to rank PICO scenarios
5. a) Scenario Validation: Assess conformance with JCA guidance
   b) Intended step in a real use case: Expert consultation panels with clinical and regulatory specialists, stakeholder engagement session with payer representatives, Delphi consensus methods for final PICO prioritization

In addition, the approach described in steps 1 to 5a was validated by simulating PICO scenario development across multiple therapeutic areas using JCA scoping exercises published by the European Commission in 2024, as part of broader efforts to refine EU HTA guidance and proactively address challenges in multinational evidence requirements. The validation presented here focuses on:

- Durvalumab in advanced hepatocellular carcinoma (aHCC)
- For validation, the "Own-PICOs" scenarios using PICO Radar™ were systematically compared to the published European Commission PICOs ("EC-PICOs")
- Comparators in each "Own-PICOs" were classified by drug class and mapped to "EC-PICOs" with the same drug class
- Outcomes were then normalized into standard categories, such as overall survival and key safety endpoints. Quantitative predictive performance was assessed by using an alignment validation score, that quantifies how closely the simulated "Own-PICOs" scenarios match "EC-PICOs" for each domain.

Results

PICOs identified to compare the new GIP/GLP-1 agonist in other IDT2DM treatments: Findings and qualitative outcomes (Table 1)

- All identified drug classes (basal/prandial insulins, GLP-1 receptor agonists, SGLT-2 inhibitors, thiazolidinediones, and combination therapies) primarily target improvements in glycemic control, as measured by HbA1c reduction, with the new GIP/GLP-1 agonist class showing the most pronounced effects on this outcome
- Secondary outcomes for these drug classes typically include weight reduction and achievement of glycemic targets
- Many drug classes (notably GLP-1 receptor agonists, SGLT-2 inhibitors, and the new GIP/GLP-1 agonist) provide cardiovascular benefits such as reduced major adverse cardiovascular events (MACE) and improved cardiovascular mortality
- Safety outcomes are generally characterized by risks for hypoglycemia (most prominent in insulins), gastrointestinal side effects (common in GLP-1 and GIP/GLP-1 agonists), genitourinary infections (SGLT-2 inhibitors), and weight gain or edema (thiazolidinediones)

Results (ctd)

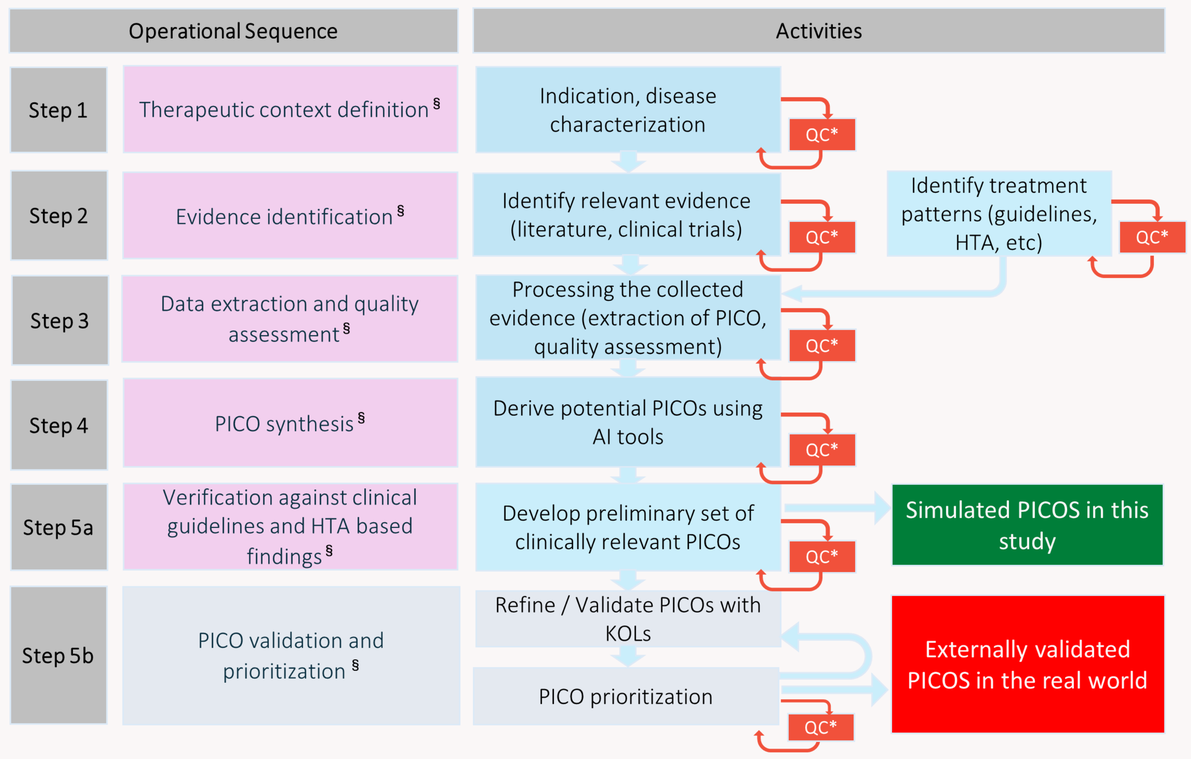
Validation of PICO Radar™

- Validation of steps 1 to 5a compared "Own-PICOs" for Durvalumab in aHCC with "EC-PICOs" scenarios, showing:
  - a strong overall alignment with HTA standards (validation score: 85.6/100) and
  - that comparator coverage and core efficacy endpoints were fully aligned (100%), while safety endpoints showed 85% concordance
  - However, quality of life assessments revealed a significant alignment gap (30/100), potentially because the PICO Radar™ tool has been applied only to research abstracts, with limited details on quality of life captured in these sources.

Conclusions

- This exercise shows that combining PICO Radar™ with human SLR expertise can provide initial, differentiated assessments and highlight outcome-specific strengths—both qualitative and quantitative—for new active substances compared to alternative PICOs
- Validation has shown that the PICO Radar™ tool offers significant potential to advance and streamline the alignment of clinical assessment scenarios with HTA requirements. The solution demonstrates robust performance in comparator selection and efficacy measurement.
- Ultimately, such a tool enhances the efficiency, consistency, and transparency of preparing for JCA submissions within the EU HTA framework

Figure 1: PICO generation process



§ Teams are supported by AI-based tools.
* Each step in the development phase is subjected to a quality check (e.g., by consulting additional sources, evaluation of the results found by medical professionals, HTA specialists) driven by human experts.

Table 1: Identified comparators and outcomes for dual GIP/GLP-1 agonist therapy in IDT2DM

Comparator	Primary Outcomes	Secondary Outcomes	Safety Outcomes
Other GIP/GLP-1 agonists (as add-on to insulin)	HbA1c reduction (e.g., -2.1%)	Weight change (-9.0 kg), HbA1c <7% target (72.1%)	Same gastrointestinal complications
Prandial Insulin (Insulin Lispro)	HbA1c reduction (e.g., -1.1%)	Weight change (e.g.,+3.2kg), HbA1c <7% target (e.g.,36.7%)	Hypoglycemia (e.g., blood glucose <54mg/dL), injection site reactions
Basal Insulin intensification (e.g., Insulin glargine / degludec)	HbA1c reduction (e.g., inferior PPG control vs new hypothetical GIP/GLP-1 agonist)	Weight change (e.g., neutral to slight gain)	Hypoglycemia risk, dose-dependent side effects
Semaglutide Weekly (add-on to insulin)	HbA1c reduction (e.g.,-1.86%)	Weight loss (e.g.,-5.7kg), MACE reduction	GI side effects (e.g., nausea, vomiting, diarrhea), pancreatitis risk
Dulaglutide Weekly (add-on to insulin)	HbA1c reduction (e.g., superior to exenatide, inferior to new hypothetical GIP/GLP-1 agonist)	Weight loss, HbA1c <7% target achievement, CV risk reduction	GI tolerability (e.g., better than exenatide), hypoglycemia risk, injection site reactions
Liraglutide Daily (+insulin degludec)	HbA1c reduction (e.g., less than new hypothetical GIP/GLP-1 agonist)	Weight loss, CV mortality reduction, HbA1c targets	GI side effects, daily injection burden, pancreatitis risk
SGLT-2 Inhibitor (e.g., Empagliflozin) + Metformin (as add-on to basal insulin)	HbA1c reduction (e.g., less than new hypothetical GIP/GLP-1 agonist)	Variable weight loss, CV death/HF hospitalization reduction	Genital infections, DKA risk, volume depletion, renal function monitoring
Pioglitazone + Insulin	HbA1c reduction (e.g.,-1.0% to -1.4%), insulin sensitization	Reduced insulin requirements, improved insulin sensitivity (HOMA-S)	Weight gain, edema, heart failure risk, bone fracture risk, bladder cancer concern
Exenatide Weekly (as add-on to insulin)	HbA1c reduction (e.g., less than dulaglutide and new hypothetical GIP/GLP-1 agonist)	Weight loss, postprandial glucose control	Higher hypoglycemia rates vs dulaglutide, GI side effects
Lixisenatide (add-on to insulin)	HbA1c reduction (e.g., modest compared to other GLP-1 RAs)	Postprandial glucose focus, limited weight benefits	Daily dosing, GI tolerability issues
Weekly Insulin Formulations (e.g., Insulin Icodec)	HbA1c reduction (e.g., non-inferior to daily basal insulin)	HbA1c <7% target achievement (e.g.,OR 1.51 vs daily insulin), improved treatment satisfaction, reduced injection burden	Higher level 1 hypoglycemia rates, similar severe hypoglycemia, comparable adverse events
Complex Triple Combinations (e.g., Metformin + SGLT-2i + GLP-1RA ± Insulin)	HbA1c reduction (e.g.,greater than monotherapy: -0.77% vs monotherapy, up to -1.75% with optimal combinations)	Significant weight loss, improved BP control, CV/renal benefits from SGLT-2i component	Higher hypoglycemia risk, increased GI side effects, complex drug interactions, higher discontinuation rates
Triple Therapy (e.g., Metformin + Sulfonylurea + Insulin)	HbA1c reduction (e.g., less than new hypothetical GIP/GLP-1 agonist)	Variable weight effects, glucose variability	Hypoglycemia (e.g., especially with sulfonylurea), weight gain, GI intolerance, not often used

Legend

- aHCC: Advanced hepatocellular carcinoma
- IDT2DM: Insulin-dependent Type 2 Diabetes mellitus
- GIP: Glucose-dependent Insulinotropic Polypeptide
- GLP-1: Glucagon-Like Peptide-1
- HbA1c: Glycosylated hemoglobin
- JCA: Joint Clinical Assessment
- MACE: Major adverse cardiovascular events
- MS: (EU) Member States
- PICO: Population, Intervention, Comparator, Outcome(s)
- QC: Quality check
- SGLT-2: Sodium-Glucose Cotransporter 2
- SLR: Systematic literature reviews

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