Development and Application of a JCA-Alignment Checklist for Early Economic Modeling in EU HTA

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BACKGROUND

The EU Joint Clinical Assessment (JCA) assesses only clinical effectiveness and safety; however, economic evaluations remain nationally governed[1] and will not be included in the JCA report. Nevertheless, the JCA's scope (particularly comparators and outcomes) will have substantial downstream consequences for national cost-effectiveness models. Research suggests that the JCA is not binding, but member states will likely incorporate JCA findings into their own HTA processes[2], and evidence gaps noted in the JCA could be leveraged during price negotiations. As a result, aligning economic models with the JCA's clinical scope is essential for efficient national submissions.

Reports and commentaries from industry and consultancy groups highlight that the JCA process introduces tight timelines and complex population, intervention, comparator and outcome (PICO) requirements. For example, an oncology JCA in 2024 produced 13 different PICOs derived from seven populations and six comparators[3]. Manufacturers have 90 days to prepare the JCA dossier after receiving the final PICO list[1] and as little as 15 days to respond to information requests[4], which runs in parallel with EMA marketing authorization processes. Early economic modeling can help manufacturers understand how different PICOs influence cost-effectiveness results and identify evidence gaps that may need to be addressed.

OBJECTIVES

1. **Develop a structured checklist to guide early economic modeling** in alignment with JCA principles.
2. **Apply the checklist in a case study** of a tumor-infiltrating lymphocyte (TIL) therapy for advanced melanoma.

METHODOLOGY

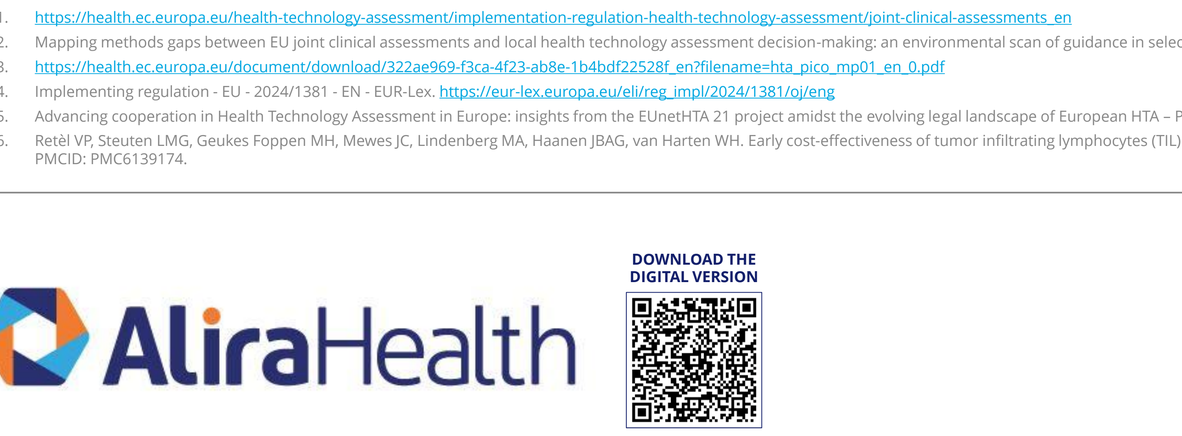
Targeted Literature Review and Checklist Development:

A targeted literature review was conducted to identify existing guidance and best practices relevant to aligning early economic models with the JCA framework. Sources included the EU HTA Regulation (EU 2021/2282)[4], EUnetHTA methodological guidelines[4], and recent JCA scoping templates published between 2023 and 2025[5]. Key principles from early modeling literature were synthesized to inform checklist domains covering PICO alignment, evidence synthesis, comparator relevance, outcome mapping, model flexibility, transferability, and transparency. The draft checklist was developed iteratively to ensure practicality and policy relevance. Expert consultation with HTA economists and JCA-affiliated stakeholders is planned to further refine and validate the checklist in future phases of this research.

Case Study Application:

The developed checklist was applied to assess a published Dutch Markov model[6] evaluating a TIL therapy versus ipilimumab in adults with advanced melanoma who had progressed following PD-1 and, where appropriate, BRAF/MEK-targeted therapies. Model inputs and structure were benchmarked against JCA PICO elements defined by national HTA agencies, including France's HAS and Poland's AOTMiT, and against EMA-labeled population data. Alignment was evaluated across key dimensions, namely population, intervention, comparator, and outcomes, to identify areas of convergence and divergence with JCA expectations.

Figure 1. Key methodological steps



RESULTS

Early Modeling JCA-Alignment Checklist Overview:

The developed checklist comprises **nine domains and over 40 criteria** (Table 1) spanning methodological, structural, and reporting dimensions. It is designed for seamless integration into early economic modelling workflows to support alignment with JCA expectations and enhance readiness for EU HTA submissions.

Table 1. Early modeling JCA-Alignment checklist domains, rationale and criteria

Checklist domains	Rationale for alignment with JCA	Key relevant steps in early economic modeling	Checklist items (criteria)
1. PICO alignment	> The JCA scope, defined through a PICO survey across member states, requires that economic models align with the final PICOs to ensure clinical inputs are consistent with the JCA evidence base.	> **Match** each **model population** to the **JCA PICOs** and ensure **consistency with EMA-label** populations and subgroups. > **Include all relevant PICO comparators** and explain any exclusions. > **Align outcome definitions** and time points with those in the JCA and clinical trials.	Population aligns with EMA-approved indication and JCA scoping templates Relevant subpopulations (e.g., treatment-naïve, biologic-experienced) identified Intervention defined per regulatory label (formulation, dosage, duration) Comparators reflect EU-wide standard of care across key markets and allows variation where necessary Outcomes match JCA-prioritized endpoints (e.g., OS, PFS, ACR, HAQ-DI, EQ-5D)
2. Evidence identification and synthesis	> EUnetHTA guidance mandates systematic reviews and valid comparison methods meeting similarity, homogeneity, and consistency assumptions, with economic models using robust clinical inputs derived from these syntheses.	> **Design systematic literature reviews in line with EUnetHTA guidance** to ensure consistency with JCA evidence standards. > **Extract comparator and outcome-specific summary statistics and uncertainty measures** to support robust early modelling. > Use validated indirect or network meta-analysis methods when direct comparisons are unavailable**, testing assumptions and incorporating prediction intervals to reflect uncertainty.**	Conduct literature review using PRISMA and EUnetHTA guidance to ensure transparent, reproducible evidence synthesis that supports early modelling Define and justify eligibility criteria aligned with JCA-relevant PICO elements to maintain consistency across synthesis and modelling inputs Assess risk of bias using validated tools (e.g., RoB 2.0) and report findings systematically to inform model assumptions and uncertainty Pre-specify and justify evidence synthesis methods (e.g., Frequentist/Bayesian NMA or ITC), including consistency checks to ensure reliable inputs for modelling
3. Comparator relevance	> EUnetHTA JCAs require comparators reflecting clinical practice across all member states, as inappropriate selection can cause misalignment and trigger re-assessment.	> **Develop a comparator matrix** mapping each population to relevant comparators across member states. > **Examine clinical guidelines and PICO survey results** to include all relevant treatments. > **Consider comparator sequencing and treatment pathways** (e.g., lines of therapy) and model switching or crossover when appropriate.	Comparator matrix developed to map each population subgroup to relevant comparators across EU member states Clinical guidelines, JCA PICO surveys, and national HTA assessments reviewed to ensure inclusion of all appropriate treatments Treatment sequencing and pathways (e.g., lines of therapy, prior treatments) analyzed to reflect real-world clinical practice Comparator justification documented with supporting evidence on clinical relevance, market availability, and current standard of care Scenario analyses conducted to address heterogeneity and crossover/switching effects where relevant to JCA comparators
4. Outcome mapping	> JCAs focus on clinical endpoints (e.g., ORR, PFS, DoR, adverse events), while economic models emphasize QALYs and ICERs, requiring careful mapping of clinical outcomes to utility and cost measures.	> **Identify clinical endpoints reported in the JCA and plan how to translate them into health-state utilities** (e.g., using mapping algorithms from ORR or PFS to utility values). > Ensure **survival models for overall and progression-free survival are consistent with JCA evidence synthesis**. > Incorporate adverse event profiles and their impact on costs and utilities.	Identify clinical endpoints prioritized in the JCA (e.g., ORR, PFS, OS, DoR) and define how each will be translated into economic model inputs Map clinical outcomes to health-state utilities using validated mapping algorithms or published utility studies Align survival modeling (for OS and PFS) with JCA-endorsed evidence synthesis, ensuring model structure and extrapolation are consistent with clinical data Incorporate adverse event profiles and quantify their impact on costs and utilities within each treatment arm Validate modeled outcomes through cross-checks against JCA results, trial data, and external real-world evidence to ensure consistency and credibility
5. Model structure and flexibility	> Because national HTA bodies will adapt the economic model, transparency and flexibility are critical. A transferable "core model" should separate clinical and cost components and allow different assumptions or parameter values for local adaptation.	> **Choose a modeling approach appropriate for the disease and interventions** (e.g., partitioned survival, Markov, or discrete-event simulation) and document structural assumptions. > **Build modular code** allowing substitution of country-specific costs, utilities and treatment patterns. > **Include scenario options** (e.g., alternative time horizons, treatment durations, stopping rules) and document how to adjust them.	Transparent, modular model architecture designed for clarity, adaptability, and reproducibility across submissions Model structure reflects disease natural history and aligns with current clinical practice and treatment pathways Time horizon, analytical perspective, and cycle length explicitly justified based on disease progression and payer requirements Multiple comparator arms incorporated to accommodate diverse JCA-relevant treatment options across member states Clinical and economic components (e.g., efficacy, resource use, costs) structured as separate, reusable layers to support updates and scenario analyses
6.Parameterization and uncertainty	> JCA guidelines stress rigorous handling of uncertainty through multiplicity, subgroup, and sensitivity analyses, which early economic models must also explore to guide evidence generation and pricing strategies.	> Use **probabilistic sensitivity analysis (PSA) with appropriate distributions** for clinical and cost parameters. > Conduct **deterministic scenario analyses varying key assumptions** (e.g., discount rates, patient mix, treatment effect durations) and structural parameters. > Consider headroom or **threshold analyses to identify the maximum price at which the technology remains cost-effective**. > Apply **value-of-information analysis** when feasible to **prioritize further research**.	Parameter inputs sourced from systematic reviews, JCA evidence synthesis, and validated real-world data, with transparent documentation of assumptions Point estimates, distributions, and correlations defined for all key parameters (clinical, cost, and utility) to enable robust probabilistic modeling Uncertainty analysis conducted through deterministic (one-way, scenario) and PSA consistent with HTA best practices Structural and methodological uncertainties explicitly tested, including model choice, extrapolation functions, and discount rates Results presented via uncertainty visualizations (e.g., CEACs, tornado plots, value-of-information analysis) to support transparent interpretation for JCA and national HTA decision-makers
7. Transferability and local adaptation	> While the JCA provides a single clinical assessment, national economic evaluations vary due to differences in comparators, resource use, and costs, so early models should anticipate cross-country heterogeneity.	> **Compile country-specific data** on clinical practice patterns, resource utilization, costs, and utility values. > For each member state, **adjust comparators and treatment sequences to reflect local standard of care.** > Develop a **mechanism to update the model** when new national guidelines or reimbursement conditions emerge.	Model inputs and assumptions adapted to reflect local epidemiology, treatment pathways, and resource use across EU member states Country-specific parameterization for costs, utilities, and comparators to ensure relevance to national HTA requirements Transferability analyses conducted to test the impact of varying local parameters on outcomes and cost-effectiveness Adaptation guidance provided to facilitate consistent application of the core model in diverse EU contexts under the JCA framework
8. Transparency and reproducibility	> The implementing regulation mandates transparent, templated dossiers and analyses, with national HTA agencies able to request underlying code and documentation.	> **Document all model assumptions**, data sources, and rationale clearly in a technical report. > **Provide code in a reproducible format** (e.g., R, Python or Excel with macros) and ensure it is sufficiently annotated. > **Create summary tables and visualizations** that link model outputs to JCA endpoints.	Full model documentation shared per EUnetHTA and ISPOR-HTA transparency standards. Version control and audit trail maintained for all parameter and structural changes. Data sources and transformation steps reported for independent verification and replication Model sharing enabled under confidentiality agreements for regulatory and HTA review
9. Stakeholder engagement and cross-functional collaboration	> The JCA process offers limited interaction with assessors. However, early engagement with clinical experts, patient groups, and HTA agencies can guide evidence generation.	> Hold **early HTA consultations** to confirm comparators and endpoints. > **Engage patients and clinicians** to validate utilities and model assumptions. > **Align trial design, RWE, and modelling** across internal teams to meet JCA needs.	Early stakeholder engagement for PICO and endpoints Cross-functional input to integrate evidence Feedback loops during synthesis and modeling Iterative dialogue for JCA alignment

TIL Early Model Case Study Findings:

The checklist application showed strong alignment between the TIL early model[6] and JCA criteria for population and intervention. However, gaps were identified in comparator inclusion, as JCA scopes recommend broader alternatives such as PD-1 inhibitors beyond ipilimumab. While the model appropriately focused on QALYs and ICERs for cost-effectiveness assessment, incorporating JCA-relevant clinical endpoints, such as ORR, PFS, and DoR, may improve alignment with the JCA's clinical focus.

LIMITATION

> This study is based on a single case example, and expert feedback collection is planned for future. Further validation across therapeutic areas is needed. As JCA guidance continues to evolve, checklist criteria may require periodic updates.

CONCLUSIONS AND IMPLICATIONS

> The JCA-alignment checklist provides a practical tool for aligning early economic models with emerging JCA expectations. Application to the TIL early model case demonstrates its value in identifying early gaps in comparator choice and outcome selection. Planned future work with expert consultation will refine the checklist further to enhance usability and ensure consistency across therapeutic areas.

> **Key implications:** better strategic alignment of early economic modeling with EU HTA processes, reduced downstream rework during national submissions, greater consistency, transparency, and transferability of evidence.

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