From PICO to Economic Evaluation: A Structured Framework for Aligning EU Joint Clinical Assessment (JCA) Evidence with National Economic Evaluations

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Ali Shajarizadeh, Nishu Gaind, Luka Ivkovic, Gopika Balasubramanian, Mir-Masoud Pourrahmat, Mir Sohail Fazeli

Evidinno Outcomes Research Inc., Vancouver, BC, Canada

Introduction

- Regulation (EU) 2021/2282 introduced the Joint Clinical Assessment (JCA), applying to new oncology medicines and advanced therapy medicinal products (ATMPs) from January 2025, and widening to orphan products in 2028 and all remaining products in scope in 2030 (**Figure 1**).[1]
- The assessment scope is defined in law as patient population, intervention, comparator(s) and health outcomes — the PICO framework [Art. 2(9); Art. 8(6)].[1]
- EUnetHTA identified nine domains by which health technologies are assessed: four clinical and five non-clinical [Recital (4)]. The JCA covers the four clinical domains (**Figure 3**).[1]
- Cost and economic evaluation is one of the five non-clinical domains [Art. 2(7)]; pricing and reimbursement remain solely a matter of national competence [Recital (14)], and JCA reports may contain no value judgement, being limited to relative effects and their certainty [Art. 9(1)].[1]
- Before the JCA, parallel assessments left health technology developers (HTDs) "confronted with multiple and divergent requests for data" [Recital (6)] (**Figure 2**).[1]
- The Regulation anticipates that Member States will require complementary analyses on populations, comparators or outcomes beyond those in the JCA report [Recital (15)].[1]

The JCA harmonises the clinical evidence package. It does not harmonise — and by design cannot supply — the inputs a national economic evaluation requires.

Objective

- To develop and demonstrate a PICO-to-economic-evaluation translation framework that maps JCA outputs to national economic evaluation requirements in five European jurisdictions (4 EU members and England & Wales), quantifies JCA coverage of those requirements, and tests whether published JCA reports deliver what the Regulation designs them to deliver.

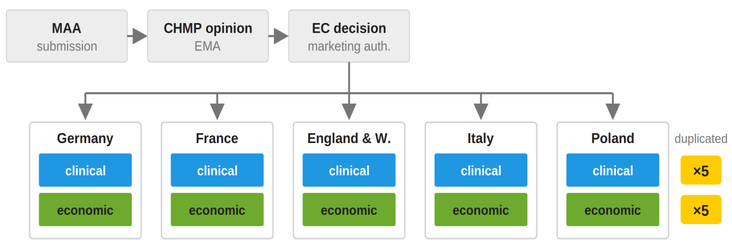
Figure 1. Phased implementation of joint clinical assessment



Regulation (EU) 2021/2282. Art. 7(2) — the scope of joint clinical assessment widens in three steps.

Scope widens in three steps under Art. 7(2). All four reports published to date fall within the first phase.[1] Abbreviations: ATMP, advanced therapy medicinal product; JCA, joint clinical assessment.

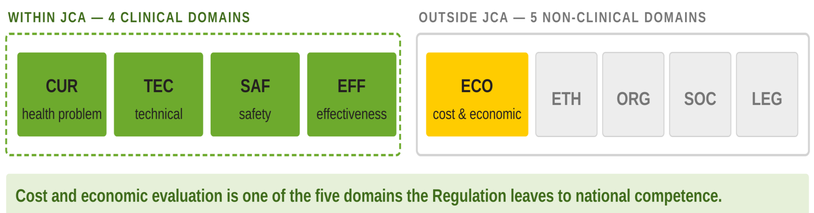
Figure 2. Before JCA: the same evidence work, repeated



Each Member State assembles its own clinical dossier and its own economic dossier from the same evidence.

One regulatory route, then five national assessments, each repeating both the clinical and the economic evidence work.[1] Abbreviations: CHMP, Committee for Medicinal Products for Human Use; EC, European Commission; EMA, European Medicines Agency; MAA, marketing authorisation application.

Figure 3. What JCA covers, and what it does not



Cost and economic evaluation is one of the five domains the Regulation leaves to national competence.

The nine EUnetHTA assessment domains. JCA covers the four clinical domains; cost and economic evaluation sits outside its scope.[1] Abbreviations: CUR, health problem and current use; TEC, technical characteristics; SAF, safety; EFF, clinical effectiveness; ECO, cost and economic evaluation; ETH, ethical; ORG, organisational; SOC, social; LEG, legal.

Methods

Design

- Two-stage study mapping national economic evaluation requirements against JCA output.
- Stage 1 mapped national requirements against what Regulation (EU) 2021/2282 states a JCA is designed to deliver.[1]
- Stage 2 tested, against all published JCA reports, whether what is designed to be delivered is in fact delivered.

Stage 1 — Parameter set

- Twenty-one parameters that a national economic evaluation must specify were compiled. Seventeen came from Heintz et al. (2016), a synopsis of 51 methodological guidelines across 25 European countries covering all five jurisdictions assessed here; their ten methodological domains were decomposed to parameter level.[2]
- Four decision-problem parameters — population, intervention and treatment positioning, comparator(s), and health outcomes — were taken from the five national guidelines, each of which requires them as dossier elements.[3–7]
- Heintz's template, in common with most European guideline synopses, contains no decision-problem item. Completeness was cross-checked against CHEERS 2022, EUnetHTA (2015) and NICE PMG36.[5,8,9]

Stage 1 — Categorisation of parameters

- Each parameter was classified once, by a single rule: does the national guideline state a value the developer adopts, or state a requirement the developer must satisfy with data or analysis?
- Specification parameters (n=11) are national conventions adopted at submission; they lie outside JCA scope by design and are reported for reference, not evaluated against the JCA (**Table 1**).
- Evidence parameters (n=10) are satisfied by data or analysis, and are evaluated against the JCA (**Table 2**). Structure was taken from Heintz et al.; values were re-extracted from current guidelines.[3–7]
- Where a cost-effectiveness analysis (CEA) is conditional rather than universal, requirements were assessed for the submission route under which an economic evaluation is triggered.
- This framework measures translation into economic evaluation only; jurisdictions placing their evidentiary demands in the clinical or added-benefit domain show few economic translation requirements by construction.

Stage 1 — Coding and metrics

- Each cell records whether the JCA supplies an evidence parameter that national guidance requires: Supplied (usable without modification), Partly supplied (subject to a country-specific constraint), Not supplied (required nationally, absent from the report), or Not required (excluded from that country's denominator).
- Denominators are therefore country-specific. For each country, across the evidence parameters it requires (R): JCA coverage ratio = S ÷ R, and unmet parameter count = R − S.
- The ratio normalises across differing denominators; the count preserves absolute number of unmet parameters. Partly-supplied parameters are reported separately and are not weighted.

Stage 2 — Application to published JCAs

- All four published JCA reports were assessed against the same evidence parameters; data cut-off 11 September 2026.[10–13]
- For each report, PICOs in the assessment scope, those addressed with comparative evidence, and the synthesis methods used were extracted.
- The first national assessment to use JCA data (NCPE Ireland, Itvisma) was examined as a validation vignette.[14]

Table 1. National specification parameters — reported for reference, not evaluated

Parameter	Germany	France	England & Wales	Italy	Poland
Required analysis type	No routine CEA	CEA / CUA	CUA	CEA / CUA / CMA	CUA
Analytic perspective	—	Collective	NHS + PSS	SSN	Public payer (NFZ)
Required outcome metric	Patient-relevant benefit	LY; QALY	QALY	QALY or natural units	QALY
Utility instrument	—	EQ-5D-5L, French tariffs	EQ-5D, UK weights	EQ-5D / SF-36 / HUI	EQ-5D (Polish)
Discount rate — costs	—	2.5%→1.5% after 30 yrs	3.5%	3.0%	5%
Discount rate — outcomes	—	2.5%→1.5% after 30 yrs	3.5%	3.0%	3.5%
Time horizon	—	Lifetime or justified	All relevant differences	Lifetime if chronic	Disease-appropriate
Cost categories	—	Direct; indirect suppl.	NHS / PSS direct	Direct SSN	Direct; indirect in SA
Acceptable evidence sources	—	RCT/MA preferred; no naive ITC	SR; randomisation preserved	Transparency of sources	Trial data + extrapolation
Presentation of results	—	CE frontier; ICER	Absolute, incremental, ICER	CE ratios	With / without indirect
Sensitivity analysis	—	DSA + PSA required	DSA, PSA, scenario	DSA; PSA advised	DSA; PSA advised

All eleven specification parameters. Germany shows no values because AMNOG runs no routine cost-effectiveness analysis; its evidentiary demands sit in the added-benefit dossier.[3–7] Abbreviations: CEA, cost-effectiveness analysis; CMA, cost-minimisation; CUA, cost-utility; DSA/PSA, deterministic/probabilistic sensitivity analysis; EQ-5D, EuroQol 5-dimension; HUI, Health Utilities Index; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; LY, life-year; MA, meta-analysis; NFZ, Polish National Health Fund; NHS/PSS, National Health Service / personal social services; QALY, quality-adjusted life-year; RCT, randomised controlled trial; SF-36, Short Form-36; SR, systematic review; SSN, Italian national health service.

Results

1. National requirements differ in kind, not only in value

- Only NICE and AOTMiT require a cost-effectiveness analysis universally.[5,7]
- Germany runs none routinely under AMNOG, where added benefit drives price negotiation.[3]
- France triggers the HAS efficiency opinion only for ASMR I–III claims with substantial budget impact.[4]
- Italy expects pharmacoeconomic analysis within TN1 negotiation types, particularly orphan medicines, with omission permitted on documented justification.[6]

A developer's first question is not how to translate JCA evidence, but whether an economic evaluation is triggered at all — a decision point preceding every parameter in this framework.

- Specification values cannot be straddled by a single model: discount rates run from France's 2.5% declining to a 1.5% floor beyond 30 years, through Italy's flat 3%, to Poland's asymmetric 5% on costs and 3.5% on effects (**Table 1**).

Table 2. JCA coverage of evidence parameters

Evidence parameter	In JCA scope?	DE	FR	E&W	IT	PL
Patient population	Yes	S	S	S	S	S
Intervention & positioning	Yes	S	S	S	S	S
Comparator(s)	Yes	N	N	N	N	N
Health outcomes	Yes	S	S	S	S	S
Indirect comparison / synthesis	Yes	P	P	P	P	P
Model type & structure	No	—	N	N	N	N
Extrapolation beyond trial	No	—	N	N	N	N
Resource use quantification	No	—	N	N	N	N
Unit costs / price source	No	—	N	N	N	N
Utility instrument & valuation	Partly	—	P	P	—	P
Parameters required (R)		5	10	10	9	10
JCA coverage ratio (S ÷ R)		60%	30%	30%	33%	30%
Unmet parameters (R − S)		2	7	7	6	7

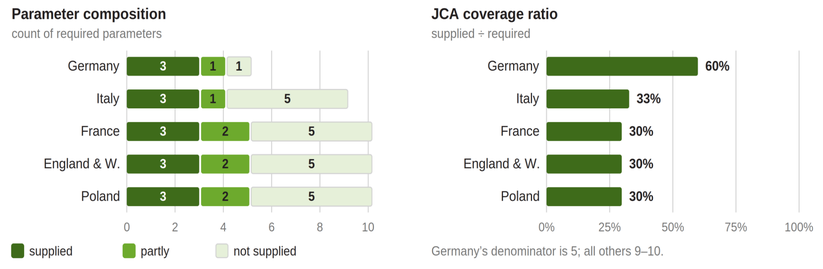
S = supplied, usable without modification · P = partly supplied, subject to a country-specific constraint · N = not supplied · — = not required by that jurisdiction, and excluded from its denominator.[1–7] Abbreviations: DE, Germany; E&W, England & Wales; FR, France; IT, Italy; JCA, joint clinical assessment; PL, Poland; R, parameters required; S, supplied.

2. JCA coverage is 30–33% wherever an economic evaluation is required

- The Regulation designs the JCA to deliver four of ten evidence parameters and to contribute to a fifth, evidence synthesis.[1]
- It delivers nothing toward model structure, extrapolation beyond trial follow-up, resource use quantification or unit costs; under Art. 9(1) it cannot.[1]
- Coverage was 30% in France, England & Wales and Poland and 33% in Italy, with six to seven unmet parameters each (**Table 2**, **Figure 4**); Germany reached 60% across five required parameters, reflecting the absence of a routine CEA rather than lower evidentiary demand.
- Comparator evidence requires adaptation to national requirements in the jurisdictions assessed; utility instruments appear in JCA scopes but are reported as clinical outcomes, never valued against national tariffs.

The gap is not jurisdiction-specific. It is structural, and near-identical wherever an economic evaluation is required.

Figure 4. Coverage and unmet parameters, by jurisdiction



Left panel preserves absolute parameter counts; right normalises across differing denominators. Derived from Table 2. Abbreviations: DE, Germany; E&W, England & Wales; FR, France; IT, Italy; JCA, joint clinical assessment; PL, Poland; R, parameters required; S, supplied.

3. Published JCAs do not reliably deliver what the Regulation designs

- Across the four published reports, 28 PICOs were defined in the assessment scopes; comparative evidence was included for 16 (57%) (**Table 3**).[10–13]
- Twelve PICOs were unaddressed, for stated reasons including no available comparator data, insufficient population overlap between intervention and comparator, and insufficient information to assess the comparator study.[10,13]
- Tovorafenib had one PICO of eight addressed, through unanchored matching-adjusted indirect comparison (MAIC) of single-arm data.[10]
- NICE requires that trial randomisation be preserved and treats comparison of single arms from different trials as observational evidence carrying increased uncertainty[5] — the method on which that single addressed PICO rests.

Where a PICO is unaddressed, the national economic model inherits no comparative estimate at all — the translation gap begins before translation does.

Table 3. What the four published JCA reports delivered, to 11 September 2026

Published JCA report	Indication	PICOs in scope	Addressed with comparative evidence	Evidence synthesis method
Tovorafenib (Ojemda)[10]	Paediatric low-grade glioma	8	**1 of 8**	Unanchored MAIC, single-arm
Lurbinectedin (Zepzelca)[11]	ES-SCLC, maintenance	1	**1 of 1**	Direct RCT (IMforte)
Tarlatamab (Imdylltra)[12]	ES-SCLC, post-platinum	7	**7 of 7**	Bucher ITC, Bayesian NMA, unanchored MAIC
Onasemnogene abeparvovec IT (Itvisma)[13]	5q spinal muscular atrophy — ATMP	12	**7 of 12**	Anchored & unanchored MAIC, Bucher ITC
All four reports		**28**	**16 of 28 (57%)**	

Addressed = comparative evidence for that PICO included in the JCA report. Six of tarlatamab's seven addressed PICOs note that not all requested outcomes were provided.[10–13] Abbreviations: ATMP, advanced therapy medicinal product; ES-SCLC, extensive-stage small cell lung cancer; ITC, indirect treatment comparison; JCA, joint clinical assessment; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; PICO, population–intervention–comparator–outcome; RCT, randomised controlled trial; SMA, spinal muscular atrophy.

4. JCA scoping can anticipate downstream economic-evaluation needs while the assessment remains clinical.

- The onasemnogene abeparvovec assessment scope specifies that health status instruments "need to be able to be converted into QALY weights to be useful in a health economic model".[13]
- Art. 9(1) bars a JCA report from economic assessment, yet Member States wrote a QALY-weighting requirement into the scope itself.[1]

The translation gap is already being managed informally, inside an instrument that formally excludes it.

5. Validation vignette — Itvisma, NCPE Ireland

- The JCA was endorsed by the Member State Coordination Group on 16 July 2026;[13] Ireland's NCPE completed the first national assessment to use JCA evidence on 16 July 2026 — the day the JCA was endorsed, 16 days after EU marketing authorisation, and seven weeks before the JCA report was published.[14]
- The NCPE used JCA evidence to inform a Rapid Review and recommended that the product not be considered for reimbursement at the submitted price; a full HTA was not recommended.[14]

The clinical question was settled jointly; the economic evaluation was performed nationally and determined the outcome.

Implications

Key findings

1. Where an economic evaluation is required, the JCA covers 30–33% of the evidence parameters a national model needs — near-identical across jurisdictions. The gap is structural, not national.
2. Only two of five jurisdictions require a cost-effectiveness analysis universally. Elsewhere it is absent or conditional, so the first evidence-planning decision is whether one is triggered at all.
3. Published JCAs addressed 16 of 28 PICOs with comparative evidence. The JCA does not reliably deliver even the four parameters it is designed to deliver.
4. Member States have written a QALY-weighting requirement into a JCA assessment scope — inside an instrument Art. 9(1) bars from economic assessment.

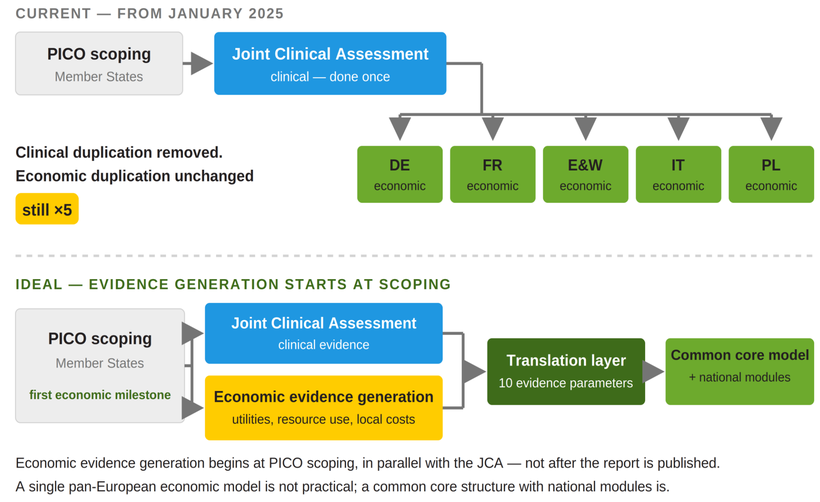
For evidence planning

- Treat the PICO scoping survey, not the published report, as the first economic-evidence milestone: the comparators entering scope determine which national models are feasible afterwards.
- Plan utility evidence independently of the JCA — health status instruments appear in assessment scopes but are reported as clinical outcomes, never valued against national tariffs; assume resource use, unit costs, extrapolation and model structure will be generated nationally in every jurisdiction.
- Check that the synthesis method the JCA will accept is one the target national body will also accept — methods acceptable within a JCA may be downgraded to observational evidence nationally[5] — and where a PICO is likely to go unaddressed for want of comparator data, identify it before the dossier rather than after the report.

Toward a defined translation layer

- A single pan-European economic model is not practical — National specifications require country-specific model settings. (**Table 1**). A common evidence platform and core model structure, adapted through national modules, is (**Figure 5**); the ten evidence parameters are a candidate specification for that layer.

Figure 5. After JCA, and the ideal state



Economic evidence generation begins at PICO scoping, in parallel with the JCA — not after the report is published.

A single pan-European economic model is not practical; a common core structure with national modules is.

Bookends Figure 2: the clinical duplication collapses into one assessment; the economic duplication does not. Abbreviations: DE, Germany; E&W, England & Wales; FR, France; IT, Italy; JCA, joint clinical assessment; PICO, population–intervention–comparator–outcome; PL, Poland.

Limitations

- Parameter counts measure the presence of a requirement, not the effort to satisfy it; a utility study and a new indirect comparison are not equivalent efforts.
- Coding reflects the authors' reading of published guidance, not agency adjudication; five jurisdictions and four reports were assessed, three of them oncology.
- The framework measures translation into economic evaluation only — Germany's low unmet count reflects where AMNOG places its demands, not lower demand overall.

Conclusions

Gaps between JCA output and national economic evaluation requirements are systematic, predictable, and concentrated in the inputs that determine the ICER. Applied at scoping rather than at submission, the framework may help reduce submission burden and improve alignment between clinical and economic evidence.

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Email: mpourrahmat@evidinno.com

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