Bridging the Evidence Gap for EU Joint Clinical Assessments

A Collaborative Framework for Robust Indirect Treatment Comparisons

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Navigating the JCA Paradigm Shift

From sequential evidence planning to an integrated, collaborative framework

The Shared Challenge
The JCA merges regulatory and HTA evidence timelines into a single window
Sequential planning — regulatory approval first, HTA second — leaves data gaps
The result: methodological uncertainty and potentially (perceived) negative assessment


The Collaborative Framework
Integrate early: embed PICO frameworks (transportable estimand structure) in Phase 2
Methodological rigour: build transparent Indirect Treatment Comparisons (ITCs)
Cross-stakeholder alignment: connect Clinical Development, HEOR and assessors early


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Harmonizing Conflicting Evidence Frameworks

Regulators ask what the treatment effect is. HTA bodies ask what that effect is worth, and against which comparator..

Regulatory Agencies		HTA Bodies
Estimand: the precise, pre-specified treatment effect being estimated, ***specified at the time of design***	›	**PICO:** population, intervention, comparator, outcome ***at the time of assessment, not design***
Central question: what is the true treatment effect?	›	**Central question:** what is the comparative value?
Focus: scientific precision	›	**Focus:** relative value
Key challenge: intercurrent events	›	**Key challenge:** the comparator

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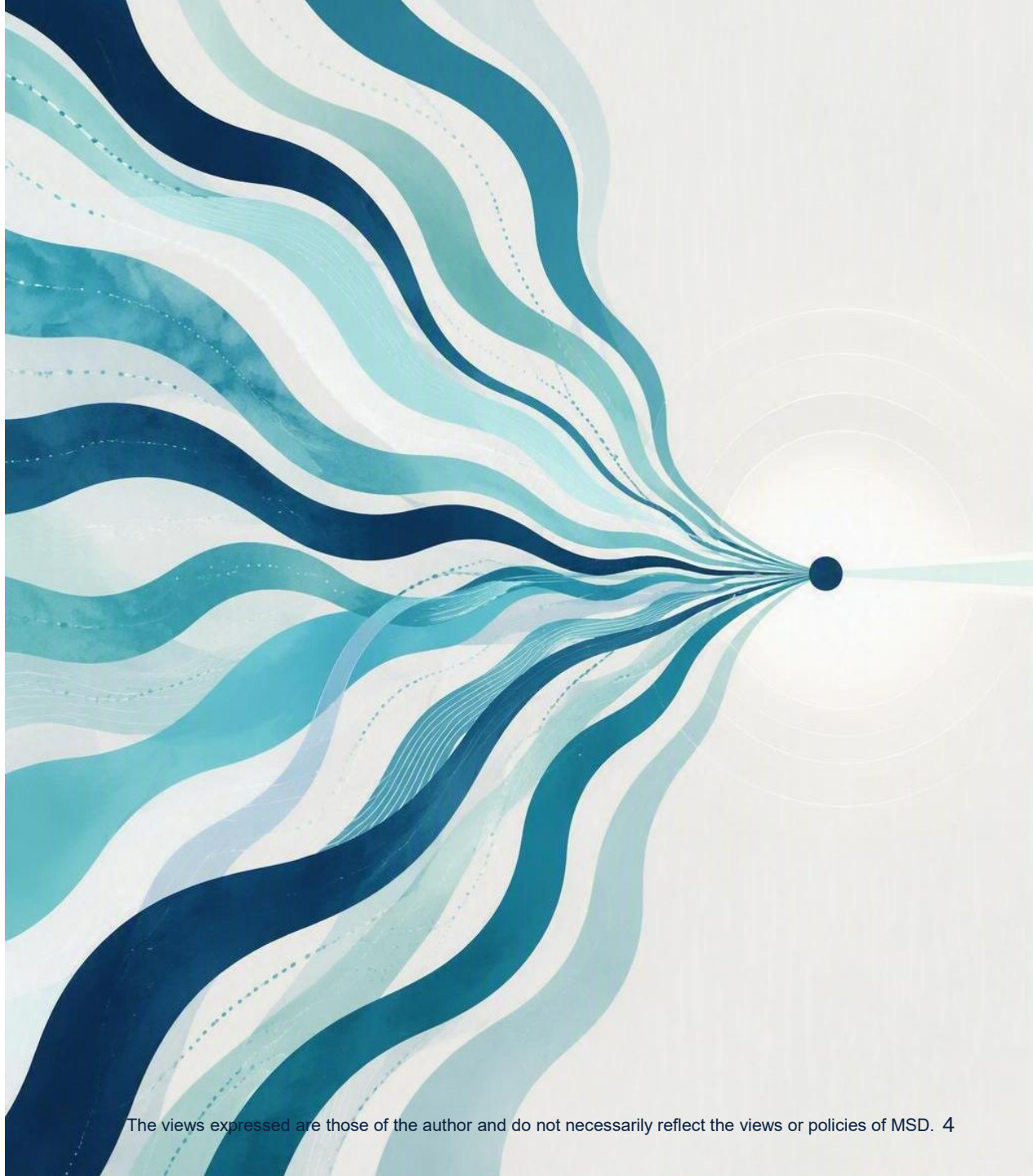
The HTA lens: PICO and the Comparator Challenge

One drug, many national comparators

- **Population:** Often narrower or broader than the licensed indication
- **Intervention:** as actually used — dose, duration, positioning
- **Comparator:** national standard of care — the hardest element to satisfy
  - One assessment, dozens of comparisons
  - Head-to-head data rarely exist for all of them
  - Indirect comparisons invite scrutiny — plan early
- **Outcomes:** survival, function, quality of life, safety,..



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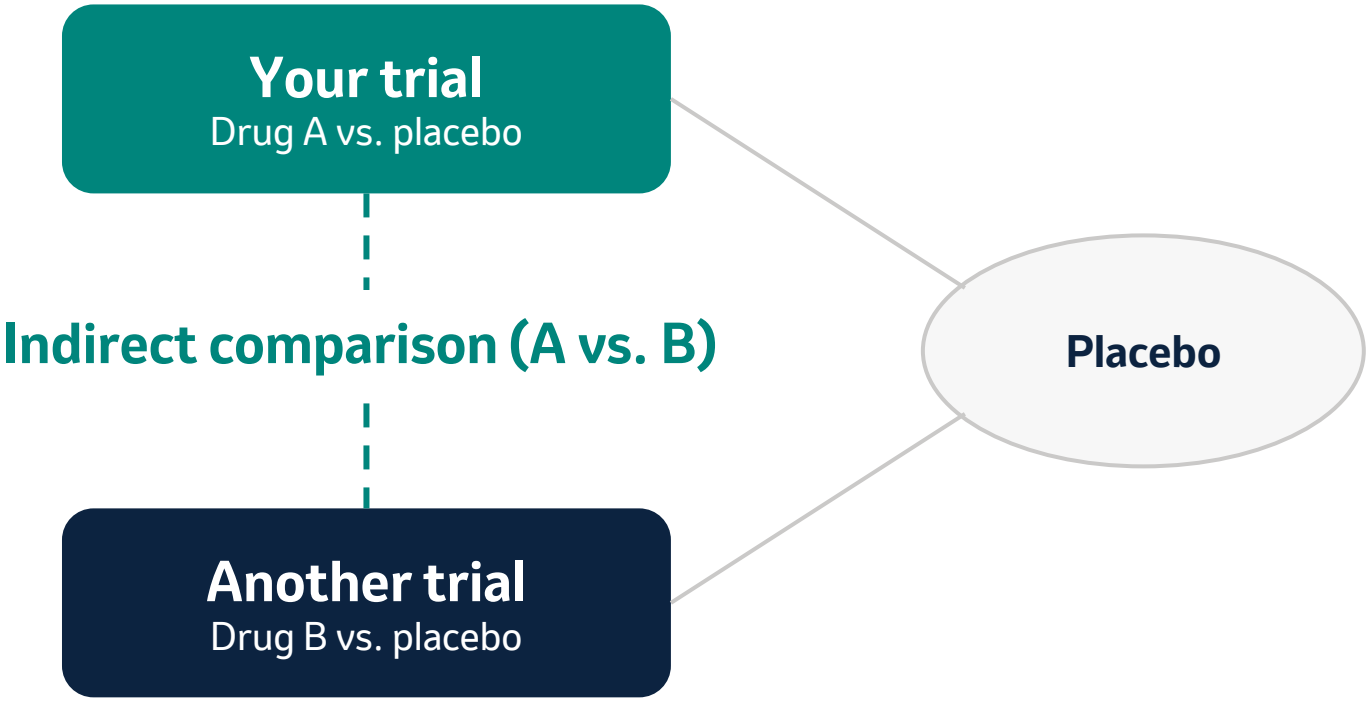
The Burden of Indirect Comparisons

Indirect treatment comparisons are necessary, and fragile



Are we comparing like with like?

Are the estimands aligned?

A ‘treatment policy’ estimand and a ‘hypothetical’ estimand do not answer the same question.

HTA bodies scrutinize population similarity, transitivity and clinical plausibility.

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Lessons from the First Joint Clinical Assessments

A recurring verdict: “high degree of uncertainty”

- Deep scrutiny of trial similarity
- Unanchored comparisons from single-arm trials judged highly problematic
- Population differences remain a concern even after statistical adjustment

- Indirect evidence is routinely rated as carrying high uncertainty
- This is not a statistical footnote — it weakens the perceived value of the medicine

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The Core Assumption of ITC — Exchangeability

If individuals in one trial were substituted into another, the relative treatment effect would be the same — assessed through three pillars

- **1. Similarity**
  - Are the trials comparable in their clinical and methodological design?
  - Assessed by comparing populations, interventions, outcome definitions and study design.
- **2. Homogeneity**
  - Is the treatment effect consistent across different studies comparing the same two treatments?
  - Assessed with forest plots, heterogeneity statistics and prediction intervals.
- **3. Consistency**
  - Does the direct evidence agree with the indirect evidence?
  - Assessed only where the network contains a closed loop of evidence.

Assessing the Similarity Assumption

Trials must be comparable across key domains

- **Population**
  - Inclusion and exclusion criteria, e.g. prior treatments and disease stage
  - Baseline characteristics, e.g. age, sex, comorbidities
- **Intervention / Comparator**
  - Dose, regimen and duration
  - Concomitant medications and background therapy
- **Outcomes**
  - Precise definition of the outcome, e.g. EFS or OS
  - Method of assessment, e.g. BICR versus investigator
  - Censoring rules and length of follow-up
  - …
- **Study Design**
  - Trial phase, e.g. Phase II versus Phase III
  - Blinding, e.g. double-blind versus open-label

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Prognostic Factors vs. Treatment Effect Modifiers

Two different roles

Prognostic Factors

- Characteristics that affect an outcome irrespective of treatment.
- Example: advanced disease stage is a poor prognostic factor for survival, whatever the treatment.
- Critical to balance in unanchored comparisons.

Treatment Effect Modifiers

- Characteristics that alter the relative effectiveness between treatments.
- Example: a biomarker may predict a better response to a targeted therapy but have no effect with chemotherapy.
- Critical to balance in all ITCs, anchored and unanchored.

How are these factors identified?

- Clinical expert opinion on the disease area and mechanism of action.
- Systematic literature review of factors reported in treatment guidelines and/or other studies.
- Analysis of existing individual patient data

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Deep Dive: Population or Matching-Adjusted ITCs (PAIC/MAIC)

Re-weighting your patients so they match the competitor's population

How MAIC works

- 1. Identify matching variables — select the key effect modifiers (and prognostic factors).
- 2. Assign weights — weight each patient in your individual patient data so the weighted averages match the competitor's aggregate characteristics.
- 3. Calculate the adjusted outcome — run a weighted analysis on your trial's outcome data.

MAIC applies when you hold individual patient data for your own trial and only aggregate data for the competitor.

Key diagnostic: Effective Sample Size

- The effective sample size falls as weighting increases.
- A low ESS signals poor population overlap — and low confidence in the adjusted result → increases uncertainty in interpretation of result.

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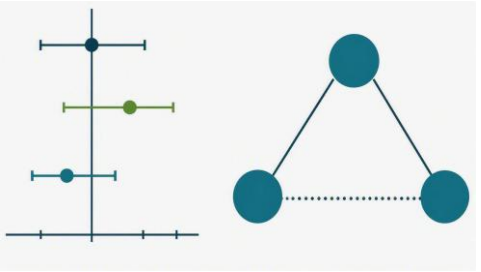
Assessing Homogeneity and Consistency

Two checks on the evidence network itself



Homogeneity
The question: is the treatment effect consistent across multiple studies comparing the same two treatments?
Can only be assessed when there are multiple trials for the same comparison.
Assessed by visual inspection of forest plots and statistical tests such as I^2 and Cochran's Q
Prediction intervals give the range within which the results of a future study might lie

Consistency
The question: does direct evidence from an A vs. B trial agree with indirect evidence via a network meta-analysis (NMA)?
Can only be assessed in networks with closed loops of evidence.
Compare the direct treatment effect estimate with the indirect estimate.
Significant differences suggest inconsistency and bias in the network.

Improving our evidence (1): A New Playbook for Process & Engagement

Acting early in development: forecast the PICO, then align through formal dialogue

Phase 1 | **Phase 2** | **Pre-pivotal** | Phase 3 | Filing & JCA



1. Plan Early (Phase 2)

Proactive PICO Simulation

The Goal: Forecast HTA needs instead of waiting for them.

The Action: Horizon scanning, analyze the comparator landscape across EU markets to identify likely PICO requirements and predict evidence gaps years in advance.



2. Talk Early (Pre-Pivotal)

Joint Scientific Consultations (JSCs)

The Goal: De-risk the development plan through formal dialogue.

The Action: Use the JSC process to get coordinated, parallel advice from both the EMA and HTA bodies. Align on trial design, comparators, and endpoints before studies are locked.

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Improving our evidence (2): A New Standard for Evidence Generation & Execution

Smarter trial design and methodological leadership to withstand JCA scrutiny



3. Design "JCA-Ready" Trials

The Goal: Create an integrated evidence plan that serves two masters.

The Action: Design trials that can support multiple estimands (e.g., a 'treatment policy' and a 'hypothetical' analysis). Embed robust, patient-centric endpoints (PROs) from the start, not as an afterthought.



4. Master the Methodology

The Goal: Lead the scientific narrative and embrace the scrutiny of ITCs.

The Action: Proactively identify Treatment Effect Modifiers/Prognostic Factors. Rigorously justify the use of advanced methods like MAIC. Build your submission around a transparent and robust argument for exchangeability.

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Thank you

Questions and discussion

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