GIPAM

NAVIGATION • EVIDENCE • IMPACT

The new Joint Clinical Assessment (JCA): What to do in the long-term and in the short-term?

ISPOR Issue Panel

November 19th, 2024, Prof. Dr. Thomas Wilke, PhD

Main HTA Evidence Needs: Overview

Evidence on medical background: Diagnostic criteria, disease stages & progression, related risk factors, current treatments, etc.

JCA	National appraisal of clinical benefits	Cost-effectiveness analyses	Budget impact modelling
"Standard" medical content around the new treatment	Data on HCRU / cost and national treatment patterns & unmet needs	Structure of CE model and defined health-states & transition probabilities	Epidemiological studies to extrapolate patient counts (incl. subpopulations)
Comparative clinical data to address consolidated PICO questions	Additional post-hoc or sensitivity analyses around the target trial	Data on natural disease history & utilities	Evidence on (local) treatment patterns
Endpoint validation evidence, if needed	Evidence on endpoint validation, benefit-risk assessment, etc.	Comparative data to be used in CE modelling, including endpoint extrapolation	Data on HCRU / cost

Source: GIPAM

Abbreviations: CE - Cost Effectiveness, HCRU – Health Care Resource Use, JCA – Joint Clinical Assessment, PICO – Population, Intervention, Comparator, Outcome

How can Comparative Clinical Evidence be generated?

Core JCA Requirement: Comparative Evidence for each defined PICO

- **P**opulation
- **I**ntervention
- **C**omparator
- **O**utcome

All EU member states will define their relevant PICO(s), meaning health technology developers could end up with more than 20 different PICOs.

How can companies generate the necessary Comparative Evidence?

OPTION A: RCTs

Very unlikely that own RCTs cover all PICOs

OPTION B: NMAs / Indirect Treatment Comparisons

Require SLRs and published evidence regarding all relevant comparators

OPTION C: Comparisons using RWE, including Synthetic Control Arm Comparisons

Is a valid option – and even uses patient-level data which is always preferred over aggregated published data

Source: GIPAM

Abbreviations: JCA – Joint Clinical Assessment, NMA – Network Meta Analysis, PICO – Population, Intervention, Comparator, Outcome, RCT – Randomized Clinical Trial, RWE – Real-World Evidence, SLR – Systematic Literature Review

With the new JCA approaching: what are the main strategic, tactical and operational tasks?

Strategy (3-4 years ahead of approval, at least 6-12 months before finalization of pivotal trial design)	**Tactics** (up to 6 months before JCA approval)	**Operations** (6 months before JCA approval until last national HTA submission/price negotiation)
Identify the (probably) relevant PICOs	Implement the Evidence Generation Plan	Develop and write your JCA dossier modules, initiate JCA process
Plan how to address each PICO, consider early scientific consultations	Keep your PICO portfolio (definition & addressing of each PICO) up to date	After JCA submission: keep relevant parts of your evidence library up to date until the last national dossier has been submitted
Develop an Evidence Generation Plan	Build your – regularly updated – evidence library	

Source: GIPAM

Abbreviations: HTA – Health Technology Assessment, JCA – Joint Clinical Assessment, PICO – Population, Intervention, Comparator, Outcome

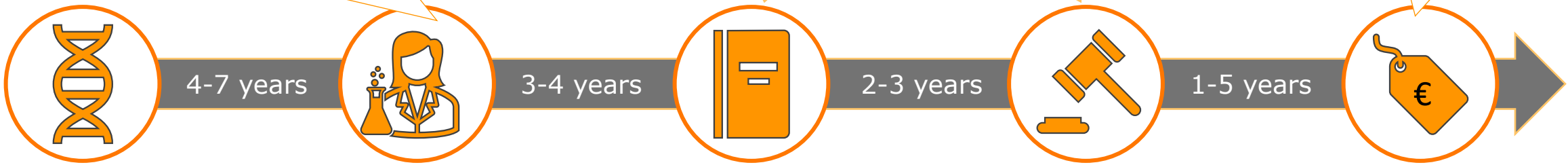
Strategic Evidence Generation Planning: When to start?

- Initiate thinking around phase 3 design & comparator
- Finalize EGP & predict PICOs ~3-4 years before regulatory submission
- Consider early scientific advice

- Evidence gap analysis for national HTAs
- Update PICOs & evidence continuously

- Final PICO announcement
- JCA dossier submission latest 45 days before CHMP opinion

In Germany, a national HTA dossier is requested by date of regulatory approval



DISCOVERY & PRECLINICAL RESEARCH

CLINICAL PHASE 1-2: HUMAN TRIALS

FILING PH. 3 PROTOCOL: PIVOTAL TRIAL

REGULATORY SUBMISSION TO EMA & JCA

NATIONAL HTA & PRICE NEGOTIATION

Length of clinical trials is driven by natural disease history and setting (acute vs. chronic care)

Timelines for national HTA & pricing decisions can be very different and delay local access for patients

Source: GIPAM

Abbreviations: CHMP - Committee for Medicinal Products for Human Use, EGP - Evidence Generation Plan, EMA – European Medicines Agency – European Union, HTA – Health Technology Assessment, JCA – Joint Clinical Assessment, PICO – Population, Intervention, Comparator, Outcome

How to do an early PICO Scoping?

Multiple sources of information should be considered to gain in-depth knowledge on PICOs:

Targeted review of clinical guidelines

Clinical perspectives of known medical conditions in terms of relevant **subtypes**, diagnostic & monitoring **measures**, and **current treatment paradigms** are widely recognized and frequently referenced in HTA decision-making.

Systematic analysis of national HTA decisions

Where HTA decisions have already been published, the **criticism should be thoroughly analyzed.**

For new indications, lessons can be learned from **analogous decisions** about technologies with similar characteristics.

Expert panels / survey based research

In disease areas that are largely uncharted, or for which structured clinical guidelines do not yet exist, direct involvement of **HCPs who are known to treat these patients in practice** is often the only way to gain further insight into PICO questions.

Source: GIPAM

Abbreviations: HTA – Health Technology Assessment, PICO – Population, Intervention, Comparator, Outcome

Example of an early PICO Scoping in ES-SCLC
according to clinical guidelines for treatment in Germany

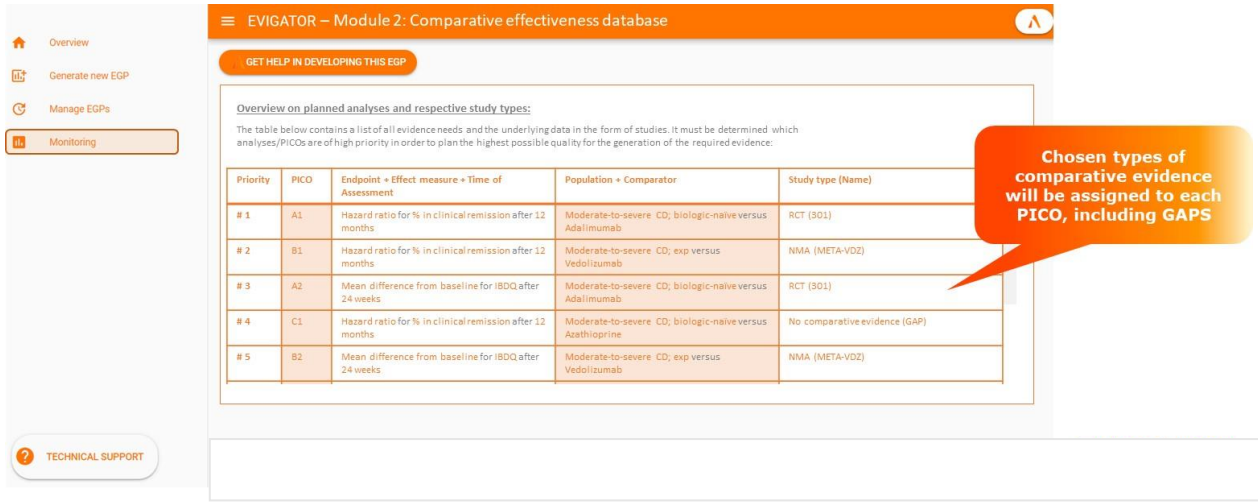
	1	2	3	4	5	6	7	8	...	40	41
Population	▪ Histologically or cytologically confirmed ES-SCLC ▪ Adults (18 years and older) ▪ No prior systemic treatment for ES-SCLC ▪ ECOG performance status (PS) 0-1 ▪ No active central nervous system (CNS) metastases			▪ Histologically or cytologically confirmed ES-SCLC ▪ Adults (18 years and older) ▪ No prior systemic treatment for ES-SCLC ▪ ECOG performance status 0-1 ▪ With active central nervous system (CNS) metastases		▪ Histologically or cytologically confirmed ES-SCLC ▪ Adults (18 years and older) ▪ No prior systemic treatment for ES-SCLC ▪ ECOG performance status 2		▪ Histologically or cytologically confirmed ES-SCLC ▪ Adults (18 years and older) ▪ No prior systemic treatment for ES-SCLC ▪ ECOG performance status 3			▪ Confirmed ES-SCLC ▪ Adults ▪ Platinum refractory disease ▪ ECOG perfor-mance status 0-2
Intervention	Novel Therapy 'XYZ' for 1L in ES-SCLC										'XYZ' for 2L
Comparator	Atezolizumab + Carboplatin + Etoposide	Durvalumab + Carboplatin + Etoposide	Durvalumab + Cisplatin + Etoposide	Cisplatin + Etoposide + Whole-brain irradiation	Carboplatin + Etoposide + Whole-brain irradiation	Carboplatin + Etoposide	Carboplatin + Paclitaxel	Paclitaxel	Carboplatin	Etoposide	Tarlatamab (future therapy option!)
Outcomes	1. Overall survival 2. Progression-free survival 3. Objective response rate			4. Duration of response 5. Symptom control 6. Health-related Quality of Life				7. Adverse events (AE) rates 8. Hospitalization rate 9. Discontinuation rate due to AEs			

Source: GIPAM

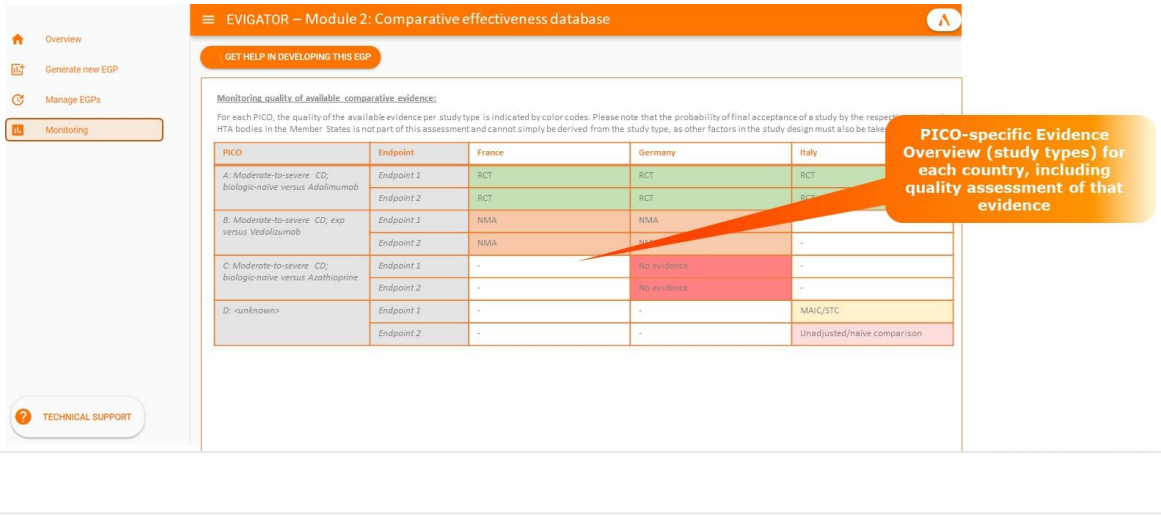
Abbreviation: AE – Adverse Events, ECOG – Eatern Cooperative Oncology Group, ES-SCLC – Extensive-Stage Small Cell Lung Cancer, PICO – Population, Intervention, Comparator, Outcome

Strategy: PICO Simulation and PICO-specific Evidence Planning in an integrated process

Which PICOs can be expected?



How to address these PICOs?



With at least 27 member states, each with different perspectives on standard of care, target populations (subgroups), and relevant outcomes, a high number of PICOs is likely.

Options for comparative study designs – per PICO: *RCT, SCA, ITCs* (MAIC, STC, or NMA), *or Evidence Gap*

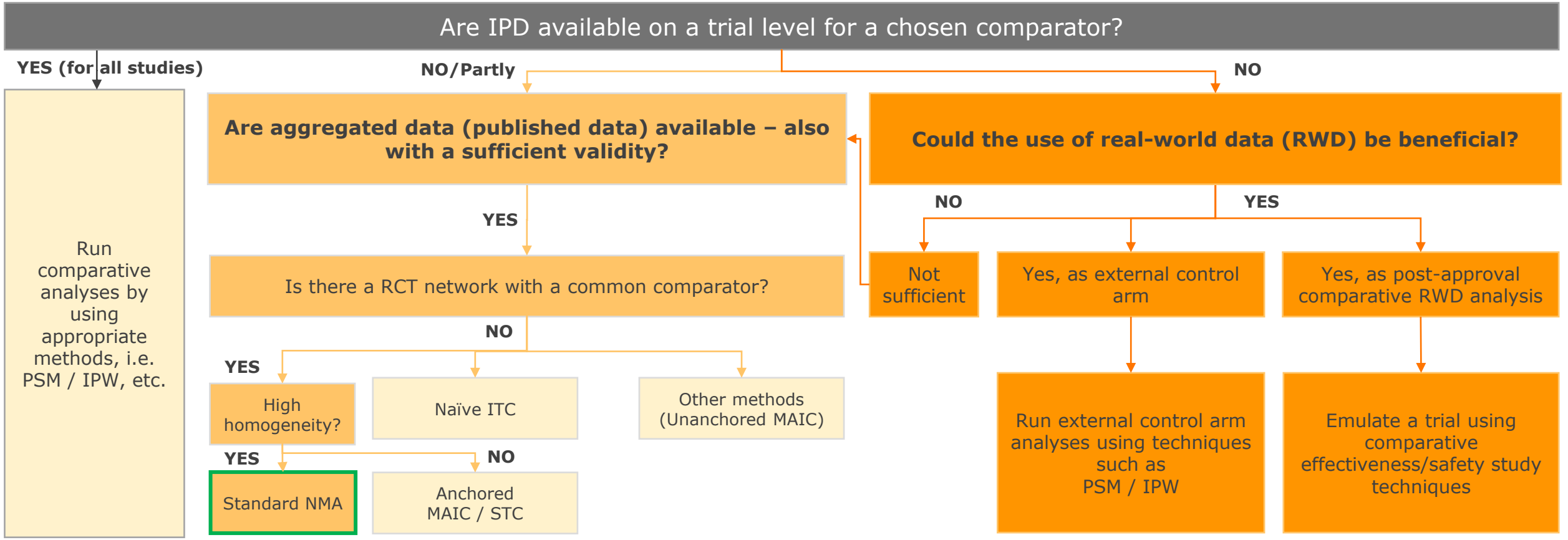
In addition, supportive evidence might be needed (e.g., endpoint validation)

Source: GIPAM

Abbreviations: ITC - Indirect Treatment Comparison, JCA – Joint Clinical Assessment, MAIC - Matching-Adjusted Indirect Comparison, NMA – Network Meta Analysis, PICO – Population, Intervention, Comparator, Outcome, RCT – Randomized Clinical Trial, RWE – Real-World Evidence, SCA - Synthetic Control Arm, SLR – Systematic Literature Review, STC - Simulated Treatment Comparison

Decision making around methods for comparative analysis in addition to RCTs

We assume: IPD are available for your asset



Abbreviations: IPD - Individual Patient Level Data, IPW - Inverse Probability Weighting, ITC - Indirect Treatment Comparison, MAIC - Matching-Adjusted Indirect Comparison, ML-NMR - Multi-Level Network Meta-Regression, NMA - Network Meta-Analysis, PSM - Propensity Score Matching, RCT - Randomized Controlled Trial, RWD - Real-World Data, STC - Simulated Treatment Comparison

Strategic Evidence Generation Plan: More than ever, due to PICO changes, a Living Document!

Medical background around TPP

- Define target population & diagnostic criteria
- Patient characterization & burden of illness
- Natural disease progression
- Treatment pathways & related outcomes
- Study types: Literature & HTA review, cohort studies, physician & patient survey, chart review & case studies

Endpoint development / validation

- Endpoint selection & prioritization
- PRO development
- Endpoint validation & definition of MCID
- Study types: Literature & HTA review, Cohort studies, Patient surveys, incl. preference studies, Guideline review & Delphi panel with physicians

Comparative evidence on efficacy & safety

- RCTs
- Pooled meta-analysis (incl. SLR)
- Standard NMA/Bucher's ITC (incl. SLR)
- SCA & observational data collection
- Population-adjusted methods (incl. SLR)
- Naïve comparison

Epidemiology

- Synthesis of epidemiological research
- Review of previous HTA submissions
- Local database studies (Population & disease registries, claims databases)

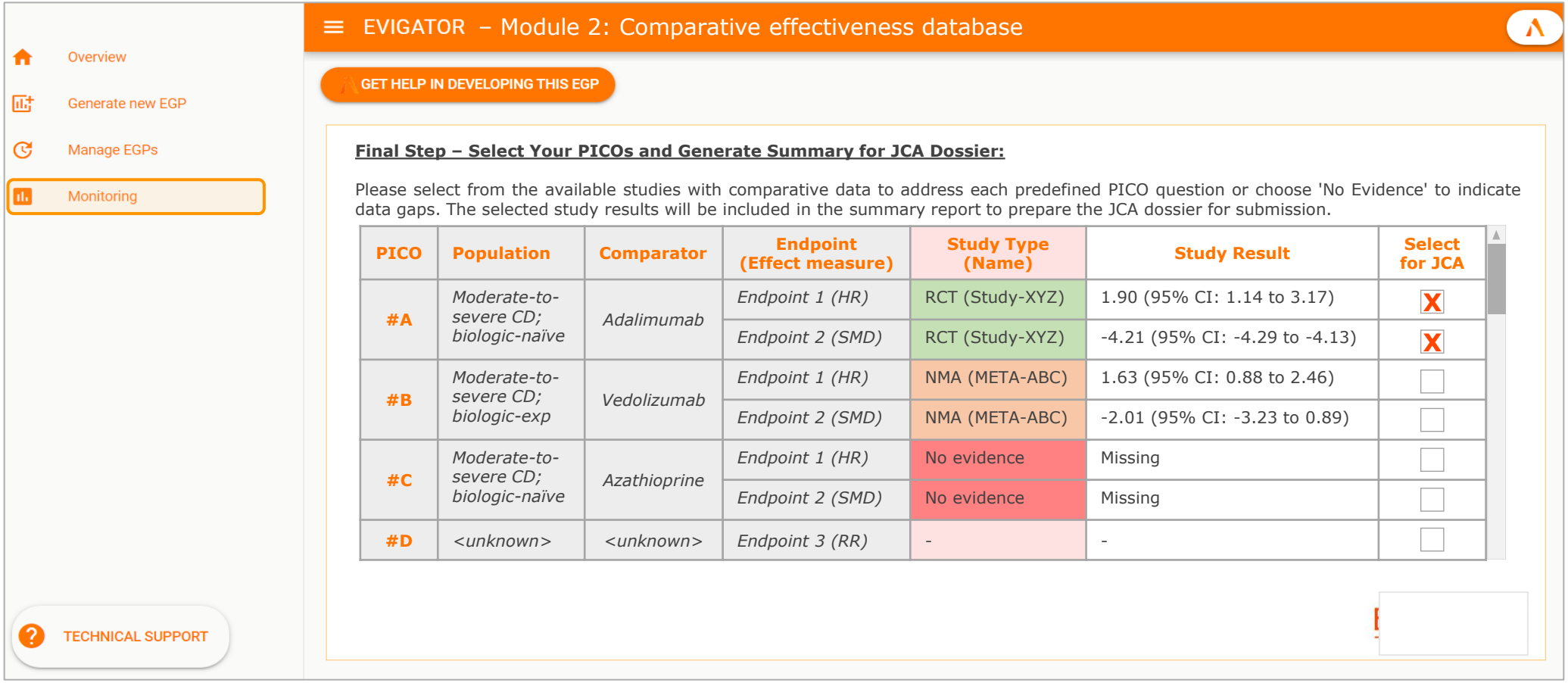
Health economic benefits

- Local HCRU/cost
- QoL gains/utilities per health-state
- Cost-effectiveness analysis & BIM
- Study types: Literature reviews & desk research, vignette studies, patient preference studies, claims data analysis, health economic modelling

Close cooperation between various cross-sectional teams (medical affairs, HEOR & RWE, global & local market access, pricing & marketing, etc.) helps!

Abbreviations: BIM - Budget Impact Model, HCRU - Healthcare Resource Utilization, HTA – Health Technology Assessment, ITC – Indirect Treatment Comparison, MCID - Minimal Clinically Important Difference, PRO - Patient-Reported Outcome, QoL - Quality of Life, RCT – Randomized Controlled Trial, TPP - Target Product Profile, SCA - Synthetic Control Arm, SLR - Systematic Literature Review

Tactics: Implement your EGP and build an Evidence Library



PICO	Population	Comparator	Endpoint (Effect measure)	Study Type (Name)	Study Result	Select for JCA
#A	*Moderate-to-severe CD; biologic-naïve*	*Adalimumab*	*Endpoint 1 (HR)*	RCT (Study-XYZ)	1.90 (95% CI: 1.14 to 3.17)	X
			Endpoint 2 (SMD)	RCT (Study-XYZ)	-4.21 (95% CI: -4.29 to -4.13)	X
#B	*Moderate-to-severe CD; biologic-exp*	*Vedolizumab*	*Endpoint 1 (HR)*	NMA (META-ABC)	1.63 (95% CI: 0.88 to 2.46)	
			Endpoint 2 (SMD)	NMA (META-ABC)	-2.01 (95% CI: -3.23 to 0.89)	
#C	*Moderate-to-severe CD; biologic-naïve*	*Azathioprine*	*Endpoint 1 (HR)*	No evidence	Missing	
			Endpoint 2 (SMD)	No evidence	Missing	
#D	*<unknown>*	*<unknown>*	*Endpoint 3 (RR)*	-	-	

Source: GIPMA

Abbreviations: CD – Crohn's Disease, EGP - Evidence, HR – Hazard Ratio, JCA – Joint Clinical Assesment, NMA – Network Meta Analysis, RCT – Randomized Controlled Trial, RR – Response Rate, SMD – Standardized Mean Difference

Tactics: Test your Evidence Library…

An Evidence Library should …	Test Questions
… structure the evidence according to study types AND PICOs	Do I always see at any time point (1) which PICOs are expected, (2) which evidence (type) is planned per PICO, (3) what the interim results are (ORs, RRs, HRs)?
… be kept updated (own trial, published evidence, RWE studies, etc.)	Is the evidence updated at least quarterly, including important NMAs / MAICs / STCs which might change due to new results of our trial, new (sub)populations, new published evidence?
… allow subgroup analyses and quick PICO changes	Can I run scenario analyses, based on my Evidence Library?
… be available to all relevant stakeholders	Do all relevant internal stakeholders have access to above information and data?

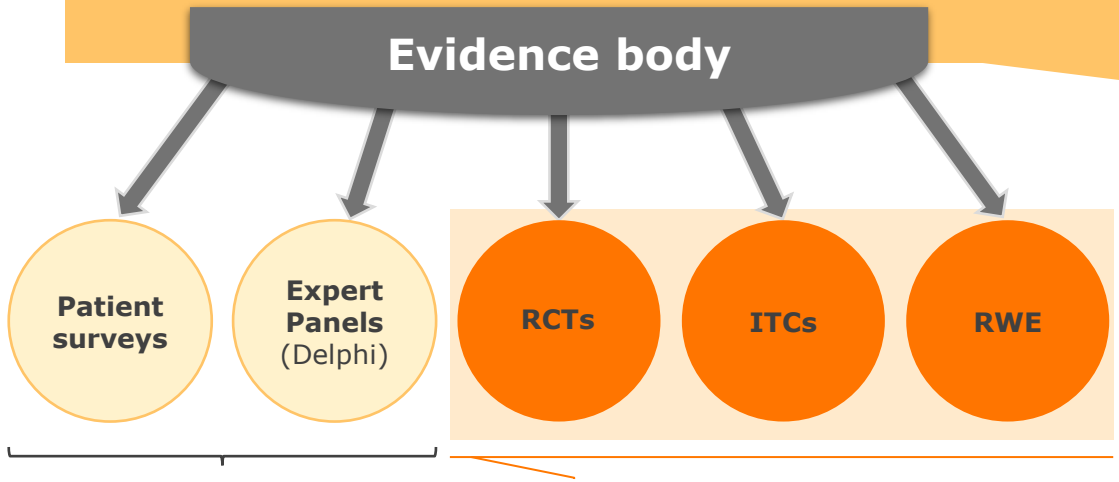
Source: GIPAM

Abbreviations: HR – Hazard Ratio, MAIC –Matching-Adjusted Indirect Comparison, NMA – Network Meta Analysis, OR – Odds Ratio, PICO – Population, Intervention, Comparator, Outcome, RR – Response Rate, STC - Simulated Treatment Comparison

Operations: Develop your JCA Dossier (I)

Do it module-based:

- One module = one PICO
- Have in mind:
  - Surrogate outcome validation
  - Bias and effect modifiers
  - Current & future SoC



Endpoint development & validation / benefit-risk assessment

Studies require regular/live updates on SoC!

Part I: Overview
- Administrative information
- Executive summary

Part II: Background
- Health problem and current clinical practice: medical condition to be treated or diagnosed
- Description and technical characteristics of the technology: medicinal product/medical device under assessment
- Information from joint scientific consultation

Part III: Research question(s) and scope

Part IV: Methods

Part V: Results
- Of information retrieval
- On relative effectiveness and relative safety

Part VI: List of References + Appendices

High-level dossier structure

Source: GIPAM

Abbreviations: ITC – Indirect Treatment Comparison, MCID – Minimal Clinically Important Difference, RCT – Randomized Controlled Trial, RWE – Real-World Evidence, SoC – Standard of Care

Operations: Develop your JCA Dossier (II)

Comprehensive description of all projects that generated the comparative evidence body:

- Description of information retrieval, including syntax for search strategies of literature review
- Full texts of references for all included studies
- Study Reports for original clinical trials and evidence synthesis studies
- Efficacy & Safety sections from EMA dossier
- Other HTA and JSC Reports, if available
- Study protocols/Statistical Analysis Plans
- Programming code for programs used for data analyses
- Listing of all ongoing related studies (incl. registries)

Evidence body is likely to be re-utilized in subsequent national HTA appraisal

➢ **Your evidence library should support that!**

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High-level dossier structure

Source: GIPAM

Abbreviations: EMA – European Medicines Agency – European Union, HTA – Health Technology Assesments, JSC – Joint Scientific Consultation

JCA Evidence Generation: Main Recommendations

Strategy	Tactics
▪ Develop initial draft PICOs 3-5 years before submission through an internal simulation	▪ Update your PICOs regularly
▪ Based on the above scoping, plan your Evidence Generation Plan at least 3-4 years prior to submission and/or pivotal trial decision ▪ Plan how to address each PICO with the relevant evidence	▪ Build an Evidence Library and keep it updated until the latest national HTA submission and/or price negotiation
▪ Implement studies, keeping in mind that some may require 2-3 years to complete.	▪ Develop the draft JCA dossier with optional elements, allowing for selection of the relevant PICOs after the official scoping process

Source: GIPAM

Abbreviations: HTA – Health Technology Assessment, JCA – Joint Clinical Assessment, PICO – Population, Intervention, Comparator, Outcome

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