A Hybrid, Multi-Source Real-World Evidence Framework for Post-Authorization Studies

Design Considerations for EU Joint Clinical Assessment Readiness

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Background

- **The mandate:** EU Health Technology Assessment (HTA) Regulation 2021/2282 makes Joint Clinical Assessments (JCAs) binding across all Member States—from 2025 for oncology and advanced therapy medicinal products (ATMPs), extending to all therapeutic areas by 2030. JCAs require real-world evidence (RWE) that is comparative, patient-centered and methodologically rigorous; studies that cannot meet JCA evidentiary standards risk delayed or restricted market authorization.
- **The gap:** Single-source observational studies cannot meet fragmented national population, intervention, comparator, outcome (PICO) requirements and carry significant risk of bias across heterogeneous EU health systems.
- **The imperative**: A hybrid, multi-source RWE framework, embedded in post-authorization study protocols, addresses this gap by integrating primary and secondary data into one coherent analysis—resolving long-term clinical uncertainty and giving HTA bodies the regulatory defensibility needed for expedited authorization pathways and outcomes-linked reimbursement frameworks.

Rationale for Hybrid Framework

Boosting site participation

Automated electronic health record (EHR) extraction harvests longitudinal secondary data without manual transcription, drastically improving site feasibility.

Navigating EU digital heterogeneity

Modular architecture adapts to varying Member State infrastructure and registry maturity without penalizing less-digitized sites.

Fulfilling patient-centric mandates

Integrated electronic patient-reported outcomes (ePRO) captures HTA-aligned health-related quality-of-life (HRQoL) and functional endpoints systematically across all sites.

Supporting active-comparator designs

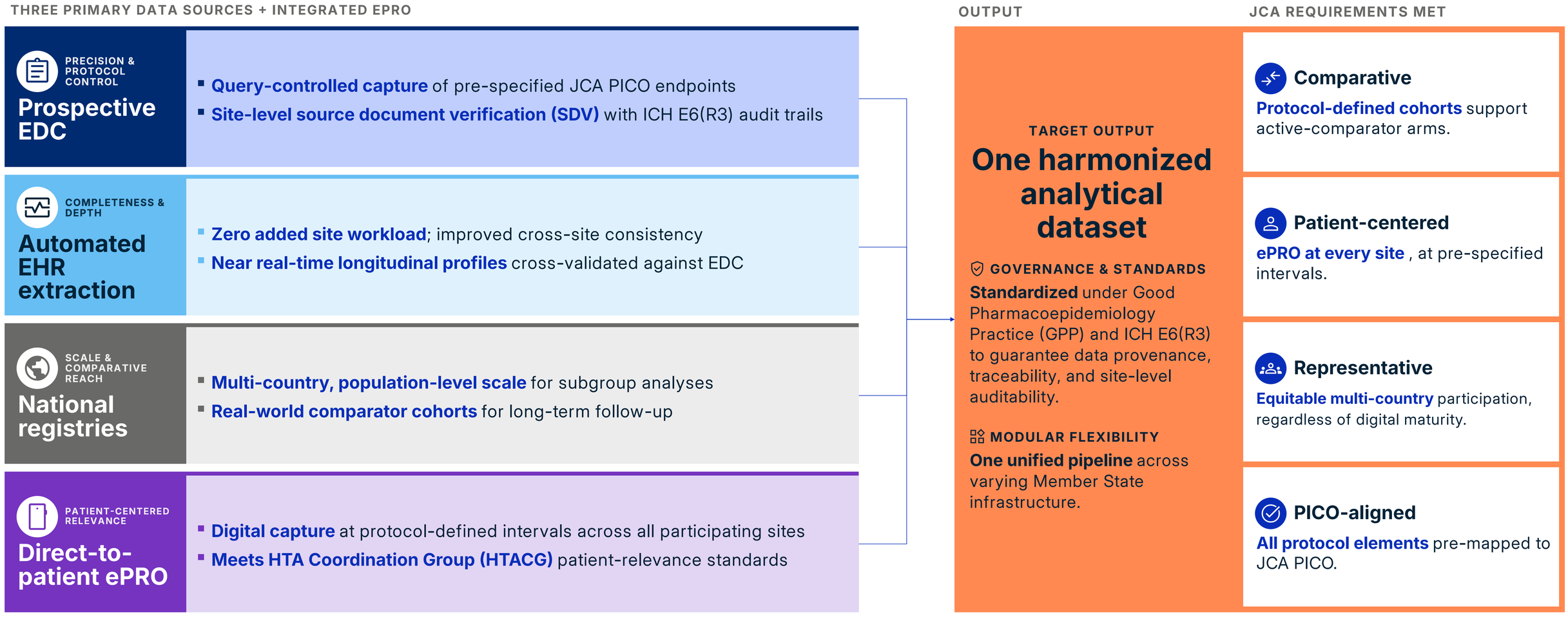
The multi-source architecture generates the population scale and data completeness that active-comparator and indirect comparison analyses require, including where indirect treatment comparisons (ITCs) or matching-adjusted indirect comparisons (MAICs) are requested by HTA bodies.

Ensuring end-to-end governance

Electronic data capture (EDC), EHR, and registry ingestion run under International Council for Harmonisation (ICH) E6(R3) and Good Pharmacoepidemiology Practice (GPP), guaranteeing the provenance and audit trails JCA assessors demand.

Multisource Architecture

THREE PRIMARY DATA SOURCES + INTEGRATED EPRO



Conclusions

A prospectively designed, **hybrid multi-source RWE framework** can generate **JCA-ready evidence** without sacrificing real-world representativeness. The modular architecture is therapeutic-area-agnostic and replicable across sponsor contexts—offering a **fit-for-purpose model** for the evolving EU regulatory landscape.

JCA-ready by design

A single, methodology-compliant dataset prospectively designed to satisfy evolving European Joint Clinical Assessment scrutiny.

Cross-country consistency

Uniform, multi-country implementation across Member States regardless of site-level health-system digital maturity.

Rigor without trade-offs

Trial-grade JCA rigor without sacrificing real-world sample scale, geographic representative-ness, or site willingness.

Broadly deployable model

A therapeutic-area-agnostic blueprint — oncology, rare diseases, neurology, cardiometabolic—applicable across the full spectrum of post-authorization evidence generation programs.

CONFERENCE
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REFERENCES
1. Regulation (EU) 2021/2282 of the European Parliament and of the Council on health technology assessment.
2. ICH E6(R3) Guideline for Good Clinical Practice.
3. ISPE Guidelines for Good Pharmacoepidemiology Practices (GPP).

ABBREVIATIONS
ATMP, advanced therapy medicinal product; EDC, electronic data capture; EHR, electronic health record; ePRO, electronic patient-reported outcomes; GPP, Good Pharmacoepidemiology Practice; HRQoL, health-related quality of life; HTA, health technology assessment; HTACG, Health Technology Assessment Coordination Group; ICH, International Council for Harmonisation; ITC, indirect treatment comparison; JCA, Joint Clinical Assessment; MAIC, matching-adjusted indirect comparison; PICO, population, intervention, comparator, outcomes; RWE, real-world evidence; SDV, source document verification.

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