HTA259

One Trial – Two Clocks

Coordinating EMA Assessment & Complementary EU HTA Evidence

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The Joint Clinical Assessment (JCA), mandated by the EU HTA Regulation (2021/2282), is closely tied to key EMA milestones, notably the EMA submission and the CHMP opinion.

While pivotal trial clinical study reports provide the foundation for regulatory decisions on efficacy and safety, they frequently lack elements required for health technology assessment (HTA). These include appropriate comparators, relevant subgroup analyses, HTA-relevant endpoints, and additional data cuts. Thus, prespecified complementary analyses and evidence syntheses are required for JCA submission.

Positive topline results of pivotal trials mark the transition from development to regulatory submission and HTA procedures. In most cases, a single pivotal trial must serve both regulatory and HTA purposes, even though the timelines and research questions differ.

- For the EMA, the research question is defined by the proposed indication provided by the applicant (HTD).
- For the JCA, the research question is defined by the assessment scope (PICOs), which reflects the needs of the European Member States, finalised 10 d after EMA d120 (LoQ). JCA dossier must be submitted no later than 45 d before the CHMP opinion.

Since the JCA dossier requires to assess the relative efficacy and safety of an intervention with respect to multiple comparators across different populations of interest, the availability of clinical data is a central prerequisite for JCA dossier preparation.

We aim to

- pinpoint where regulatory and HTA evidence-generation intersect,
- quantify timing gaps, and
- identify practical levers for delivering HTA-ready analyses.

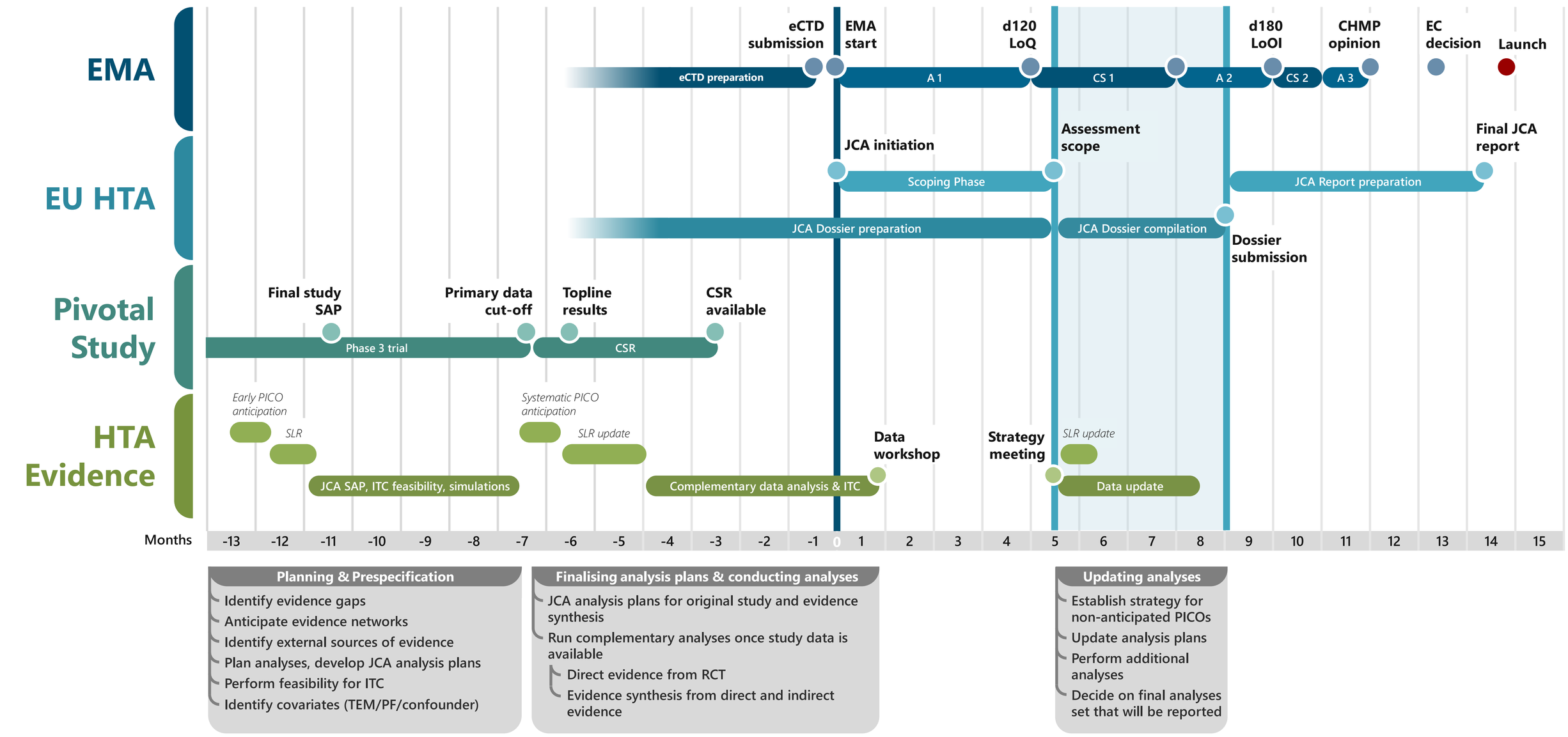

Figure 1 Overlay of EMA and JCA Milestones with Strategic Action Points

“Preparation is Key”

The short timeframe between PICO scoping and JCA dossier submission limits opportunities for late-stage adjustments in statistical analyses, unless preparation starts early.

In practice, about three months remain to align analyses to the assessment scope, update SLR, include further evidence, and compile the dossier. This time can be used productively when planning and prespecification are in place.

By anticipating PICOs early, performing gap analyses based on the SAP, and prespecifying complementary HTA analyses in a dedicated JCA SAP, manufacturers can ensure readiness, while limiting work at risk.

Early consultations, ITC feasibility assessment, and identification of external evidence sources further strengthen preparedness. With agilely allocated resources and defined decision pathways, even last-minute scope changes can be managed effectively.

We assessed the availability of pivotal trial data, CSRs, and complementary HTA analyses in five German HTA (AMNOG) procedures from five HTDs in the field of cardiovascular disease and oncology (figure 2).

While CSR data are typically available about three months prior to EMA submission, HTA-specific analyses are generally conducted subsequently and may require several additional months to complete. In our dataset, complementary analyses were completed after an average of 13.3 months (95% CI 11.8-14.8); a timeframe that is unlikely to be feasible under JCA conditions.

This is due to a range of demanding tasks that must not be underestimated: calculation of subpopulations, alternative operationalization of endpoints, responder analyses, extended PRO evaluations, consideration of additional data cuts, and comparative evidence synthesis including meta-analyses and ITCs.

There is considerable potential to reduce this time gap through proactive planning and prespecification; nevertheless, the actual workload and the number of required analyses can be substantial.

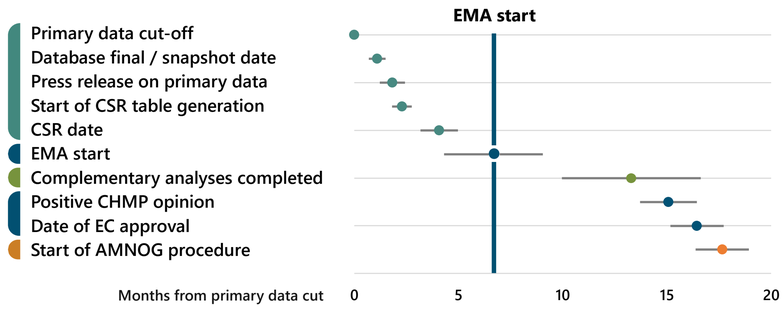

Figure 2 Availability of pivotal trial data, CSR and complementary HTA analyses *in relation to EMA timelines (Type 2 variations) and the start of AMNOG procedures across 5 projects from 5 different HTDs.*

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References
REGULATION (EU) 2021/2282 on health technology assessment: https://eur-lex.europa.eu/eli/reg/2021/2282/oj/eng; Commission Implementing Regulation (EU) 2024/1381: https://eur-lex.europa.eu/eli/reg_impl/2024/1381/oj/eng

Abbreviations
A: assessment; CHMP: committee for medicinal products for human use; CI: confidence interval; CS: clock stop; CSR: clinical study report; JCA: joint clinical assessment; EC: european commission; eCTD: electronic common technical document; EMA: european medicines agency; HTA: health technology assessment; HTD: health technology developer; ITC: indirect treatment comparison; LoOI: list of outstanding issues; LoQ: list of questions; PF: prognostic factor; PICO: population, intervention, comparator and outcome; PRO: patient-reported outcome; RCT: randomized controlled trial; SAP: statistical analysis plan; SLR: systematic literature review; TEM: treatment effect modifiers