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Health Solutions

Qualitative and Quantitative Evidence Synthesis Strategies to Support JCA and IRA Submissions

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INTRODUCTION

The Inflation Reduction Act (IRA) and the accompanying Drug Pricing Negotiation (DPN) in the United States (US) were signed into law in 2022. The European Union's (EU's) Joint Clinical Assessment (JCA) was outlined in 2018 and final implementation was released on 23 May 2024. There are substantial differences between evidence synthesis requirements for the JCA versus IRA. The JCA guidance applies to new oncology medicines and advanced therapies (i.e., cell and gene therapies) for 2025; the guidance will apply to therapies for rare diseases starting January 2028 and for all new medicines starting January 2030. The IRA DPN applies to products approved or licensed in the US for 7 (small-molecule drugs) or 11 years (biologics).

OBJECTIVES

- To detail evidence synthesis requirements for JCA and IRA submissions
- To describe the use of artificial intelligence (AI)–assisted platforms for more efficient evidence synthesis that may be used to support JCA and IRA submissions

The IRA DPN Program and Evidence Synthesis Requirements for IRA DPN Submissions by Manufacturers:

- ✔ Negotiations for the first 10 products have been completed, and the negotiated prices were released in August 2024, reflecting discounts between 38% and 79% from 2023 list prices.
- ✔ The Centers for Medicare and Medicaid Services (CMS) will select the next 15 products for negotiation by **1 February 2025**. Submission of information requested in the Information Collection Request will be **due by 1 March 2025** (i.e., manufacturers and other stakeholders have 1 month to prepare evidence for submission to CMS).
- ✔ As with the first set of drugs, participating drug companies with a selected drug for the DPN program and the public will have the opportunity to submit evidence and information on the selected drugs and their therapeutic alternatives to CMS.
- ✔ DPN guidance requires an evidence-enabling comparison of clinical and other benefits (e.g., caregiver perspectives and productivity) for a given treatment versus its primary comparators.
- ✔ Submissions require careful consideration of comparators and relevant outcomes, changes in symptoms or patient-reported outcomes (PROs), changes in productivity and quality of life, and caregiver perspectives for a given product and indication.

Table 1. CMS IRA and JCA DPN Program: Information Required From Manufacturers

IRA		JCA	
Evidence from manufacturer	**Evidence identified by literature review** (REQUIRES LITERATURE REVIEW AND EVIDENCE SYNTHESIS)	**Evidence from manufacturer**	**Evidence identified by literature review** (REQUIRES LITERATURE REVIEW AND EVIDENCE SYNTHESIS)
• Selected drug information • Information for nonfederal average manufacturer price • Research and development costs and recoupment • Current unit costs of production and distribution • Prior federal funding • Patents, exclusivities, and approvals • Market data and revenue and sales volume data	• Off-label use • Potential therapeutic alternatives • Use in treatment and clinical comparative effectiveness evidence for the drug and potential therapeutic alternatives • Prevalence of indication among the Medicare population, Medicare utilization, and cost estimates • **Therapeutic advance and unmet medical need:** Extent to which the selected drug represents a therapeutic advancement compared with existing therapeutic alternatives and the extent to which the selected drug addresses an unmet medical need • **Specific populations and patient experience:** Identify any specific populations that are impacted by the selected drug and/or its therapeutic alternatives and describe how they are impacted. Identify any considerations related to access, social drivers of health and health-related social needs, health equity, and/or health disparities that are relevant to the indication, selected drug, and/or its therapeutic alternatives	• Information about the medicinal product under assessment and the health technology developer • Previous assessments under the EU HTA regulation • Characterization of the medicinal product, including regulatory status • Ongoing or planned compassionate use programs • Other marketing authorizations	• Characterization of the medical condition (may be supplemented with information from patients and experts) • Characterization of the target patient population and clinical management pathways (may be supplemented with information from patients and experts) • Prevalence and incidence in the different states • Relative effectiveness and relative safety according to the assessment scope; results to be presented by PICO

Table 2. Evidence Synthesis Requirements for Submissions by Manufacturers

	IRA (REQUIRES LITERATURE REVIEW AND EVIDENCE SYNTHESIS)	JCA (REQUIRES LITERATURE REVIEW AND EVIDENCE SYNTHESIS)
Approach	Qualitative evidence synthesis of data is collected via an SLR. DPN guidance does not specify that a meta-analysis should be conducted, but a meta-analysis may potentially be used to demonstrate comparative effectiveness.	Only clinical evidence is required for the JCA, and such evidence will be identified using an SLR, which may be used to generate comparative efficacy estimates. The SLRs are based on the PICO framework and selection of relevant PICOs is of primary importance (Figure 2). The selection process of the SLRs should be documented in flowcharts (i.e., PRISMA) with reasons provided for exclusions at both the abstract and title screening and the full-text screening. Additional SLRs, such as to identify prognostic factors and effect modifiers, also may be required.
Data elements	SLRs may be conducted to determine key comparators and to gather data on clinical benefits and safety, PROs, productivity, and caregiver perspective.	Clinical evidence (efficacy and safety) should be identified.
Sources of evidence	Publicly available, peer-reviewed literature is preferred by CMS, rather than poster abstracts and non–peer-reviewed literature. When providing non–peer-reviewed literature, the manufacturer must provide sufficient information on these for CMS to assess their applicability to the DPN.	The SLR should include searches of electronic databases, trial registries, and HTA reports; it also should include information on trials sponsored by the manufacturers. Both peer-reviewed and non–peer-reviewed literature should be included.
Cost-effectiveness evidence	CMS does not use quality-adjusted life-years or any evidence from comparative effectiveness research in a manner that treats extending the life of an individual who is older in age (> 65 years), disabled, or terminally ill as of lower value than extending the life of an individual who is younger, not disabled, or not terminally ill. Published cost-effectiveness studies can be included as evidence of drug benefit.	The JCA does not require evidence of cost-effectiveness.

HTA = health technology assessment; PICO = population, intervention, comparator, and outcome; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR = systematic literature review.

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Use of AI-Assisted Platforms in Evidence Synthesis:

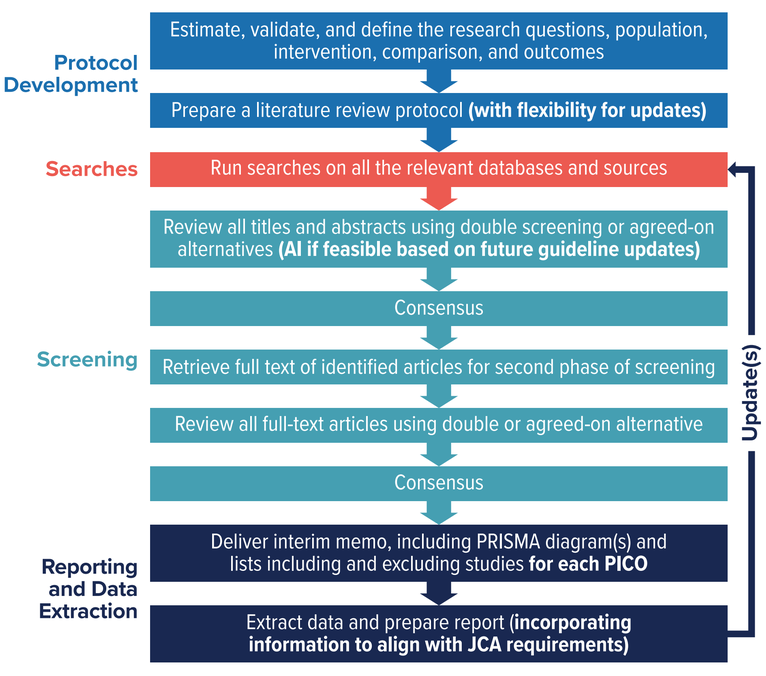
- AI systems have been used for several key steps in the SLR process and are generally divided into search strategy, screening of records, data extraction, and critical appraisal (or risk of bias). In addition, AI may be used for estimation of PICOs for JCA, which will be a key initial step to define the research questions.
- Several SLR software tools (see Figure 1) currently offer AI augmentations for specific steps within the review process. Although no system offers full automation of SLRs, these software tools integrate AI recommendations into expert workflows to accelerate the process.
- Whereas guidance from the EU and US bodies specifically with respect to AI in the evidence synthesis process remains to be developed, recent AI guidance has emerged from the National Institute for Health and Care Excellence (NICE),[1] which covers the method of recommended use of AI systems and notes that NICE will need to approve the use of AI for SLRs.
- Recommended use of AI in evidence synthesis is as an augmentation, not replacement, of expert work. The guidance and associated recommendations[2] also support methodological transparency and, where possible, validation of AI tools.
- Acceptable use of AI systems in the context of IRA- and JCA-related evidence synthesis includes compliance with all applicable methodological guidance. Within this, AI tools may assist with suggesting PICOs, search terms or strings, performing extraction of PICOs based on inclusion and exclusion criteria, data extraction of interventions and outcomes, and critical appraisal assessments.
- Time savings and high levels of accuracy with some validation exercises have been demonstrated when using AI augmentations in screening[3] and extraction[4] and may be appropriate for IRA- and JCA-supporting research workflows, depending on the anticipated accuracy for the research question and future acceptability across guidelines.
- In summary, there is promise in using foundation models to support a range of tasks required in SLRs, but the use of large language models (LLMs) to augment human work in SLRs presents several limitations. These include potential inaccuracies in the output, such as errors in classifying abstracts or in extracting data, as well as the generation of erroneous citations. Although LLMs can achieve reasonable accuracy compared with human-performed tasks, there remains a need for continuous human oversight and validation.

Figure 1. Current State of AI Augmentation in Leading SLR Software

	Search Strategy	Screening	Data Extraction	Critical Appraisal
Fern.ai	✔	✔	✔	
Nested Knowledge	✔	✔	✔	
DistillerSR		✔	✔	✔
EPPI-Reviewer		✔	✔	✔
Laser AI		✔	✔	✔
PICO Portal		✔	✔	✔
Abstrackr		✔		
Covidence		✔		

Note: Commercially available SLR software tools offering AI augmentations for specific steps in the SLR process. Feature availability is based on software documentation.

Figure 2. Schematic Presentation of Our Systematic Review Process for JCA



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