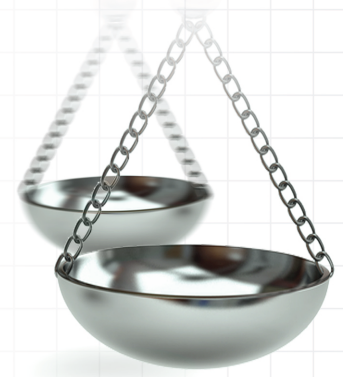




R WE ready for reimbursement? A round up of developments in real-world evidence relating to health technology assessment: part 20

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In this update, we examine Canada's Drug Agency position statement on artificial intelligence in evidence generation, a systematic review of clinical trial data linkage approaches, and real-world effectiveness evidence from England's respiratory syncytial virus vaccination program.

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Canada's Drug Agency (CDA-AMC) released its position statement on the use of artificial intelligence (AI) in evidence generation and reporting in April 2025 [1], drawing heavily on the National Institute for Health and Care Excellence (NICE) position statement [2,3] while adapting it for the Canadian health technology assessment (HTA) context. Like NICE, CDA-AMC outlines potential AI applications across the evidence generation spectrum: systematic reviews could benefit from automated search strategies and data extraction; clinical evidence generation might use AI for trial optimization and synthetic data creation; real-world data (RWD) analysis could leverage natural language processing for unstructured data; and cost–effectiveness evidence could employ AI for economic model development and validation.

The core principles between the two organizations are remarkably aligned. Both emphasize that AI methods should only be used when there is demonstrable value, with potential benefits carefully balanced against risks including algorithmic bias, cybersecurity threats and reduced transparency. Both agencies stress the importance of human augmentation rather than replacement, requiring capable and informed humans to remain 'in the loop' throughout AI-assisted processes. Early engagement with the respective agencies is encouraged when organizations are considering AI methods, and both position statements emphasize the need for clear justification of AI use with transparent reporting of assumptions and limitations. Both organizations classify the use of AI for estimating comparative treatment effects (causal inference) as particularly high-risk because model mis-specification or latent-variable bias can materially distort effect estimates, potentially leading to harmful reimbursement decisions. Recommended safeguards include prospective analytic plans, negative-control outcomes and robust sensitivity analyses.

CDA-AMC has made several adaptations to reflect the Canadian environment. The definition of AI has been updated to align with Canada's proposed Artificial Intelligence and Data Act (AIDA), which describes AI as enabling computers to "*learn to complete complex tasks by recognizing and replicating patterns identified in data*" [4]. The statement indicates that users must comply with the forthcoming AIDA legislation expected to become law in 2025. The organization has developed its own evaluation instrument for AI search tools to assist evidence synthesis producers, demonstrating practical implementation of their position. Like NICE, CDA-AMC plans to monitor AI use in evaluations and update the position statement as new evidence emerges.

The convergence of these position statements reflects a growing international consensus on AI governance in HTA. Both recognize AI's transformative potential while acknowledging the critical need for rigorous oversight, transparency and ethical considerations. As AI methods continue to evolve rapidly, manufacturers and evidence generators should anticipate that decision maker expectations will similarly evolve, requiring ongoing attention to best practices and emerging standards across different jurisdictions. For manufacturers seeking to understand how AI can be practically applied in health economic and outcomes research workflows, a recent comprehensive primer by Reason *et al.* provides essential guidance on using generative AI, particularly large language models, for health economics applications [5]. The primer covers practical implementation through application programming interfaces (APIs) and prompt engineering, and addresses critical considerations around security, validation and ethical use.

Beyond frameworks for AI governance, the practical integration of different data sources continues to evolve as a critical component of modern evidence generation. Clinical trials, while remaining the gold standard for establishing treatment efficacy, have participants who continue to interact with healthcare systems long after trial completion. These ongoing interactions create valuable data trails in electronic health records, administrative databases, insurance claims, disease registries and vital statistics that traditionally remain disconnected from trial data. This separation represents a significant missed opportunity, as the combination of rigorously collected trial data with comprehensive RWD could provide valuable insights into treatment effectiveness, safety and economic impact. The concept of linking clinical trial data to routinely collected healthcare data sources has gained momentum as healthcare systems have become increasingly digitized. However, the practical implementation of such linkage approaches faces numerous technical, regulatory and logistical challenges that have limited widespread adoption. Najafzadeh *et al.* conducted a systematic scoping review to understand how clinical trial data linkage has been implemented in practice, examining 71 studies published between 2016 and 2023 that reported successful linkage of trial participants to external data sources [6]. The geographic distribution of linkage studies reflects the infrastructure requirements for successful implementation. The USA led with 32.4% of studies, followed by the UK at 29.6%. This pattern highlights the importance of robust national health data systems, standardized patient identifiers, and regulatory frameworks that support data linkage while protecting privacy. The data sources most commonly linked to trial data were administrative claims databases (57.7% of studies), followed by electronic health records and laboratory data (23.9%), and disease registries or vital statistics (18.3%). The review identified several primary use cases for trial data linkage, each addressing specific limitations of traditional trial designs.

Post-trial long-term follow-up emerged as the most common application (31.0% of studies), addressing the fundamental limitation that most trials have relatively short observation periods due to cost and logistical constraints. Validation of routinely collected data represented another major application (23.9% of studies), where trial data serve as a gold standard for assessing the accuracy and reliability of administrative or registry data. This application is particularly valuable for establishing the credibility of real-world evidence (RWE) sources for regulatory and HTA purposes. The use of linked data to capture primary or secondary trial outcomes (26.8% of studies) represents an innovative approach to trial design that can reduce data collection burden and costs while potentially improving outcome ascertainment. Similarly, the measurement of healthcare resource utilization and costs provides economic data that is often not captured in traditional trial designs. The review found that linkage success rates varied dramatically across studies, ranging from 0.3 to 100% of trial participants successfully linked to external data sources. Most studies employed deterministic linkage methods using direct patient identifiers such as National Health Service numbers, Medicare numbers or social security numbers. Approximately 45% of studies obtained consent for linkage prospectively as part of the main trial, while a similar proportion (46.5%) received waivers of authorization from ethical review boards for retrospective linkage. Privacy-preserving record linkage (PPRL) is a technique that can match records from many data sources across institutions and jurisdictions without directly sharing personally identifiable information. Unlike the traditional linkage methods found in the reviewed studies, which typically required direct access to identifiable patient data and were often limited to single-country implementations, PPRL could enable manufacturers to conduct multijurisdictional linkage studies without the complex data sharing agreements and privacy compliance challenges that currently restrict such work. However, the authors noted that no study employed emerging privacy-preserving technologies such as PPRL or tokenization. This likely reflects the timing of the studies reviewed, as many were initiated before these methods became widely discussed, but suggests significant opportunities for future implementation as these approaches mature.

In a HTA setting, the linkage of trial data with RWD may help for conditional reimbursement/managed access agreements where long-term outcomes need to be assessed. For pharmaceutical manufacturers, the evidence

supporting clinical trial data linkage presents both opportunities and implementation challenges. The potential for reduced data collection costs, extended follow-up periods and enhanced economic evidence could significantly improve the value proposition of clinical development programs. However, successful implementation requires careful planning and expertise. Early consideration of linkage possibilities during trial design can optimize the potential for successful implementation. The need for prospective consent in some jurisdictions means that linkage opportunities must be considered during initial trial design rather than as an afterthought. The emergence of PPRL could substantially reduce the regulatory and logistical barriers that currently limit linkage studies, potentially enabling manufacturers to implement linkage across multiple jurisdictions without the complex consent and data sharing arrangements required by current approaches. While methodological advances in data linkage create new opportunities for evidence generation, the need for these approaches is exemplified by informative data generated by recent real-world effectiveness studies.

Respiratory syncytial virus (RSV) is a significant public health challenge, particularly affecting vulnerable populations including young infants and older adults [7]. There is a significant burden of RSV illness on National Health Services during winter months. Recent advances in RSV vaccine development have led to the approval of several vaccines for older adults. The UK's vaccination strategy took a cautious, evidence-based approach. Following comprehensive review by the Joint Committee on Vaccination and Immunisation (JCVI), the UK initially recommended vaccination for individuals aged 75–79 years using the bivalent prefusion F (pre-F) vaccine (Abrysvo[®], Pfizer) from 1 September 2024, and then a routine program for those turning 75 years old [8]. This targeted approach differed from broader recommendations in other countries and reflected careful consideration of cost–effectiveness and clinical need. In order to investigate the real-world effectiveness of the vaccine, researchers from the UK Health Security Agency conducted an early assessment of England's RSV vaccination program [9]. The study analyzed data from 1 September 2024, through 6 January 2025, covering the initial months of the vaccination rollout. The researchers utilized national databases including the Second-Generation Surveillance System for RSV PCR test results, the Emergency Care Dataset for hospital admissions and the Immunization Information System for data on vaccination. The study population comprised 2.54 million individuals aged 75–79 years who became eligible for vaccination, with researchers comparing hospitalization rates across age groups (70–84 years) to identify the impact of vaccine eligibility. The researchers employed a regression discontinuity design to isolate the causal effect of vaccine eligibility on RSV hospitalization rates. This methodological approach was particularly valuable because it leveraged the sharp age cutoff at 75 years to create a natural experiment. The regression discontinuity design compares outcomes between individuals just above and below the eligibility threshold, capitalizing on the assumption that people aged 74 years and 11 months are fundamentally similar to those aged 75 years and 1 month, except for their vaccine eligibility status. This quasi-experimental design minimizes confounding factors that might otherwise bias the results, as the assignment of eligibility based on age is effectively random with respect to other characteristics that influence RSV risk. Under the continuity assumption that underlying RSV risk changes smoothly with age, any discontinuous jump in hospitalization rates observed at the 75-year threshold can be attributed to the causal effect of vaccine eligibility rather than other age-related factors. Key findings showed that vaccine coverage reached 47.4% by the study's end, with coverage ranging from 45.0% in 75 years old to 48.9% in 79 years old. Most importantly, the analysis revealed a 30% reduction (95% CI: 18–40; $p < 0.0001$) in RSV associated hospitalizations among vaccine eligible individuals compared with the expected rate without vaccination. This RWE provides crucial validation of prelicensure clinical trial data and supports JCVI recommendations for RSV vaccination in older adults. While this study was not conducted by the manufacturer, the relatively rapid generation of RWE (within months of program launch) demonstrates the feasibility of conducting timely post-market effectiveness studies, and will become more and more important to demonstrate the value new therapies are providing to health systems.

These recent developments illustrate the evolving landscape of real-world evidence generation, from regulatory frameworks governing AI use to innovative data linkage methodologies and rapid real-world effectiveness studies. For manufacturers, these developments emphasize the importance of early planning for post-market evidence generation, and leveraging emerging technologies and methods to enhance the value and timeliness of real-world evidence studies.

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