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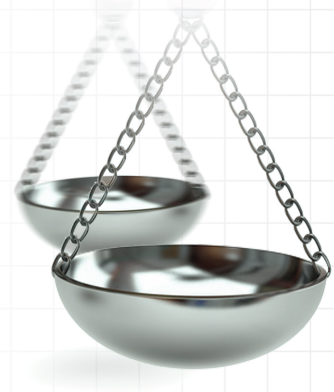

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R WE ready for reimbursement? A round up of developments in real-world evidence relating to health technology assessment: part 19

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In this update, we examine a checklist for real-world evidence use in Medicare drug price negotiations under the Inflation Reduction Act, a review of health technology assessment reassessments across major health technology assessment agencies, and two complementary studies that used natural experiment approaches to explore the relationship between herpes zoster vaccination and reduced dementia risk.

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The Inflation Reduction Act (IRA)'s Medicare Drug Price Negotiation Program represented a watershed moment in US healthcare policy, empowering the Centers for Medicare & Medicaid Services (CMS) to negotiate prices for medications [1]. The first negotiation cycle ended in late 2024 with ten Part D drugs having maximum fair prices effective from January 2026 [2]. In January 2025 the CMS selected 15 additional Part D drugs for the second negotiation cycle, with negotiated prices taking effect in 2027. To determine the maximum fair price for selected drugs, CMS considers evidence across multiple dimensions, including: therapeutic advance relative to alternatives, comparative effectiveness across clinical and patient-reported outcomes, impact on specific populations, and ability to address unmet medical needs [1]. This evaluation framework creates an opportunity for real-world evidence (RWE) to complement clinical trial data, particularly since IRA negotiations occur 7–11 years post-launch – a timeframe when substantial real-world data (RWD) has typically accumulated. Despite this opportunity, it is not clear yet how CMS are using RWE for decision making. Tunis *et al.* make a compelling case for how CMS can use RWE [3]. For identifying therapeutic alternatives, RWE captures evolving treatment patterns that may differ from the comparator used for initial clinical trials. For evaluating therapeutic advances, RWE can be used to compare a medication to newer treatments that become available over time, and to also understand treatment impacts on patient reported outcomes and healthcare resource use and effects in specific populations that were less represented in clinical trials (for example the elderly). The authors acknowledge that RWE has limitations and if best practices are not followed results are not robust enough for treatment effect estimation. To ensure that CMS can assess a RWE study and to help manufacturers conduct high-quality studies, Tunis *et al.* have developed a structured checklist specifically designed for the Medicare Drug Price Negotiation context. Their checklist was developed through a systematic four-step process: identifying IRA requirements for price determination, assessing which provisions could be supported by RWE, reviewing existing best-practice guidelines and consolidating these guidelines through author consensus. The resulting framework provides manufacturers with clear guidance on reporting key metrics across four domains: relevance of evidence (how does the study apply to IRA decision making), study design (describe the study design using best practice templates e.g. HARPER [4]), study quality (list the best practice methodology guideline followed, potential biases and how these were addressed) and study validation (for example, publication in a peer-reviewed journal). For pharmaceutical manufacturers, this article hopefully should stimulate

the proactive planning of RWE generation for medicines that may eventually qualify for price negotiation. There are now many RWE guidance documents from regulators, HTA agencies, medical societies and academics [5]; however, this checklist may provide a framework for ideating studies to demonstrate the value of a medicine to CMS. Given that this checklist reflects the perspectives of the authors, clear guidance from CMS on how they will consider and evaluate RWD would be important to further encourage high-quality evidence generation.

Building on this potential for RWE in price negotiations, it is also important to understand how health technology assessment (HTA) agencies are incorporating RWD throughout the product lifecycle. HTA agencies increasingly recognize the need to evaluate products at multiple points across their lifecycle to understand their evolving value. This has led many agencies to implement processes for reassessment. HTA reassessments (HTARs) assess a product after its initial reimbursement recommendation, often as part of a managed entry or conditional reimbursement agreement. RWE is a potential tool to inform these reassessments by complementing clinical trial evidence and addressing uncertainties identified before and after launch. Jaksa and colleagues conducted a targeted review to identify recently published HTARs and characterize the use of RWE [6]. They selected six major HTA agencies: the Canadian Agency for Drugs and Technologies in Health (CADTH, now Canada's Drug Agency [CDA-AMC]), the National Institute for Health and Care Excellence (NICE; England, UK), Haute Autorité de Santé (HAS; France), Gemeinsamer Bundesausschuss/Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (G-BA/IQWiG; Germany), Zorginstituut Nederland (ZIN; The Netherlands) and the Pharmaceutical Benefits Advisory Committee (PBAC; Australia). They screened each agency's online database to identify recent HTARs published between January 2018 and October 2023, extracting data on drug characteristics, HTAR details, initial assessment details and if/how RWE was used. The researchers identified 40 HTARs across the six agencies, with over half (55%) being for oncology therapies. Most HTARs (70%) were requested by the HTA agency, with sponsors requesting reassessment in 20% of cases to expand indications, remove prescribing restrictions, or update information relevant for price negotiations. The majority of HTARs (58%) resulted in no change in patient access. A total of 22 of the HTARs used RWE (55%), but often evidence submitted to address uncertainties included both clinical trial data and RWE. HTARs using RWE had a higher prevalence of orphan therapies (77%) compared with those that did not use RWE (22%). Among the 22 HTARs that used RWE, the evidence was used to address at least one clinical uncertainty, with most uncertainties relating to primary (33%) and secondary (31%) end points. G-BA/IQWiG relied heavily on clinical trial data alone, whereas other agencies were more open to considering RWE alone. In general, RWE alone was more likely to be included to address economic uncertainties; Registry data was the predominant RWD source (57%), with limited use of electronic health records (10%) and claims data (4%). Sponsors provided most of the RWE studies (57%), though in some cases agencies generated their own evidence (27%). Notably, no *de novo* RWE comparative effectiveness studies were identified, despite agencies previously noting these could serve as valuable evidence. This may be because the HTA agency did not request this or the short timeframe of reassessments which may not allow sufficient data accumulation for studies; nevertheless, it seems to be a missed opportunity. The potential of RWE in HTARs therefore is likely currently not being fully realized. HTA agencies could update their current RWE guidance documents to specify when high-quality RWE would be most valuable for addressing specific uncertainties in reassessments and allowing longer data collection periods could enable more mature RWD to inform reassessments. Manufacturers should consider investing in high-quality RWE studies and engaging early with HTA agencies to align on evidence needs and feasible timelines for data collection. Collaboration between manufacturers and HTA agencies throughout the product lifecycle is essential to ensure that reassessments are informed by the most robust evidence possible, ultimately serving both patients and health systems.

While the previous studies highlight RWE applications in formal assessment processes, innovative methodological approaches are also advancing our understanding of treatment effects in real-world populations. In previous parts of this series, we have described how causal treatment effects can be obtained from RWD using the target trial approach [7–11]. However, other methods exist, for example natural experiments or instrumental variables, which are called out in RWE frameworks such as that from NICE [12]. Natural experiments are situations where exposure to treatment is determined by factors outside a researcher's control but resembles random assignment. This is valuable for causal inference in observational studies because they minimize bias, allowing researchers to make stronger causal claims with non-experimental data. Examples include policy changes, natural disasters or arbitrary rules that create treatment and control groups. Two recent studies have leveraged this approach to provide compelling evidence that herpes zoster vaccination may significantly reduce the risk of developing dementia in older adults. Varicella-zoster virus is a herpes virus that causes chickenpox (varicella) and shingles (herpes zoster). Given the risk of serious

complications from shingles, vaccination is now recommended for older adults in many countries. There is evidence to suggest that herpesviruses may be involved in the etiology of dementia, but this has not yet been conclusively proven. Taquet and colleagues tried to investigate this association by leveraging a natural experiment created by the transition from live attenuated to recombinant shingles vaccine in the US [13]. The researchers used data from electronic health records and propensity-score matching to compare over 100,000 individuals who received their first dose of shingles vaccine between November 2017 and October 2020 (predominantly recombinant vaccine) to individuals who received their first dose between October 2014 and September 2017 (predominantly live vaccine). Results showed that individuals in the group that predominantly received the recombinant vaccine had a 17% lower risk of developing dementia over the following 6 years. A negative control outcome showed no difference, and both shingles vaccines were also associated with lower risks of dementia compared with influenza and tetanus–diphtheria–pertussis vaccines. This effect was stronger in women than men. Eyting and colleagues published a complementary study that utilized a different natural experiment approach with the live attenuated herpes-zoster vaccine [14]. Their research exploited the fact that in Wales (UK), starting on 1 September 2013, those born on or after 2 September 1933 were eligible for herpes-zoster vaccination for at least 1 year, while those born earlier never became eligible. Using electronic health records from approximately 80% of primary care providers in Wales, they compared adults born just before versus just after this eligibility cutoff. Being born just 1 week after the cutoff caused an abrupt increase in vaccination probability from 0.01 to 47.2%. The researchers then used this 'quasi-randomization' in a regression discontinuity analysis to show that the herpes-zoster vaccine reduces shingles diagnoses, and that vaccination reduces the probability of a new dementia diagnosis over a 7-year follow-up by approximately a fifth. The vaccine did not affect other common causes of mortality or morbidity beyond shingles and dementia, nor did it increase uptake of other vaccinations or preventive health measures. The findings remained consistent when using alternative analysis approaches. The effect was also considerably stronger among women than men, which may have biological plausibility as off-target effects of vaccines are sex dependent. These studies provide a rare example of consistent findings across two methodologically distinct but rigorous RWE investigations, strengthening the case that herpes-zoster vaccination may represent an effective strategy to reduce dementia risk in older adults. Both studies leveraged policy-based natural experiments to overcome the healthy-vaccinee bias that often limits observational vaccine studies. For manufacturers the studies illustrate how innovative RWE study designs can generate compelling causal evidence on intervention effects that traditional clinical trials might miss or be unable to address. Indeed, GSK is undertaking a similar approach with EPI-ZOSTER-110, a quasi-experimental study analyzing adults following the UK Shingles Vaccination Program expansion, which created a natural randomization by making 65-year-olds immediately eligible for GSK's Recombinant Zoster Vaccine while delaying eligibility for 66-year-olds until age 70. If the causal relationship between herpes zoster vaccination and reduced dementia risk is confirmed, this preventive intervention could significantly mitigate the enormous and growing economic and social burden of dementia on healthcare systems worldwide.

These recent developments highlight the diverse applications of RWE across the healthcare landscape – from informing policy-level price negotiations to supporting reassessment of treatment value post-launch and identifying unexpected therapeutic benefits through innovative study designs. For manufacturers, payers and regulators alike, embracing high-quality RWE generation throughout the product lifecycle will be increasingly essential for demonstrating value and supporting evidence-based decision making.

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References

1. Beattie A, Treharne C, Mardiguian S, Ramagopalan SV. Access in all areas? A round up of developments in market access and health technology assessment: part 2. *J. Comp. Eff. Res.* 12(12), e230162 (2023).
2. Ramagopalan SV, Pannelay AJ. Access in all areas? A round up of developments in market access and health technology assessment: part 7. *J. Comp. Eff. Res.* 14(6), e250043 (2025).
3. Tunis SR, Shafrin J, Than KS, Whittington MD, Willke RJ, Bharmal M. Use of real-world evidence in the Medicare Drug Price Negotiation Program: a checklist for the Centers for Medicare and Medicaid Services and manufacturers. *Health Aff. Sch.* 3(3), qxaf030 (2025).
4. Bray B, Ramagopalan SV. R WE ready for reimbursement? A round up of developments in real-world evidence relating to health technology assessment: part 11. *J. Comp. Eff. Res.* 12(5), e230008 (2023).
5. Castanon A, Tsvetanova A, Ramagopalan SV. RWE ready for reimbursement? A round up of developments in real-world evidence relating to health technology assessment: part 16. *J. Comp. Eff. Res.* 13(8), e240095 (2024).
6. Jaksa A, Arena PJ, Hanisch M, Marsico M. Use of real-world evidence in health technology reassessments across 6 health technology assessment agencies. *Value Health* S1098-3015(25)00090-7 (2025).
7. Arora P, Ramagopalan SV. R WE ready for reimbursement? A round up of developments in real-world evidence relating to health technology assessment: part 18. *J. Comp. Eff. Res.* 14(4), e250014 (2025).
8. Bray BD, Ramagopalan SV. R WE ready for reimbursement? A round up of developments in real-world evidence relating to health technology assessment: part 14. *J. Comp. Eff. Res.* 13(1), e230189 (2024).
9. Arora P, Ramagopalan SV. R WE ready for reimbursement? A round up of developments in real-world evidence relating to health technology assessment: part 17. *J. Comp. Eff. Res.* 14(1), e240212 (2025).
10. Castanon A, Bray BD, Ramagopalan SV. R WE ready for reimbursement? A round up of developments in real-world evidence relating to health technology assessment: part 15. *J. Comp. Eff. Res.* 13(5), e240033 (2024).
11. Simpson A, Ramagopalan SV. R WE ready for reimbursement? A round up of developments in real-world evidence relating to health technology assessment: part 7. *J. Comp. Eff. Res.* 11(10), 699–701 (2022).
12. National Institute for Health and Care Exellence (NICE). NICE real-world evidence framework. ECD9. Overview. (2022). Available at: https://www.nice.org.uk/corporate/ecd9/chapter/overview
13. Taquet M, Dercon Q, Todd JA, Harrison PJ. The recombinant shingles vaccine is associated with lower risk of dementia. *Nat. Med.* 30(10), 2777–2781 (2024).
14. Eyting M, Xie M, Michalik F, Heß S, Chung S, Geldsetzer P. A natural experiment on the effect of herpes zoster vaccination on dementia. *Nature* doi: 10.1038/s41586-025-08800-x (Epub ahead of print) (2025).