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THE INFLATION REDUCTION ACT AND ITS IMPLICATIONS ON REAL-WORLD EVIDENCE

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An Axtria Point of View

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WHAT IS THE INFLATION REDUCTION ACT (IRA)?

The Inflation Reduction Act (IRA), passed in August 2022, aims to reduce prescription drug prices for Medicare beneficiaries in the United States. This legislation introduces three significant reforms[1]:

- Medicare Prescription Drug Program (Part D): Changes will impact how prescription drugs are covered under Medicare Part D
- Inflationary Caps in Medicare (Part B): Sets limits on price increases for Medicare Part B services, aiming to control costs and enhance affordability
- Medicare Price Negotiation: Pharmaceutical companies will need to adapt their evidence presentation methods, which allows Medicare to negotiate drug prices directly

These reforms significantly affect evidence generation and presentation within the pharmaceutical industry. The Medicare Drug Pricing Negotiation Program (DPNP) establishes maximum fair price (MFP) guidelines for certain drugs. Starting in 2026, Medicare Part D will negotiate prices for drugs delivered in outpatient settings. This initiative seeks to improve access and affordability for beneficiaries.[2]

THE TEN DRUGS SUBJECT TO PRICE NEGOTIATION UNDER THE IRA

As Medicare and manufacturers negotiate, they will consider each drug's clinical benefits, unmet clinical needs, and impacts on Medicare beneficiaries. Starting in 2026, Medicare Part D will begin price negotiations for an initial list of ten drugs spanning diseases such as diabetes, heart failure, and rheumatoid arthritis. These drugs include[3]:

- Apixaban (Eliquis)
- Empagliflozin (Jardiance)
- Rivaroxaban (Xarelto)
- Sitagliptin (Januvia)
- Dapagliflozin (Farxiga)
- Sacubitril/valsartan (Entresto)
- Etanercept (Enbrel)
- Ibrutinib (Imbruvica)
- Ustekinumab (Stelara)
- Insulin aspart (Fiasp, Fiasp FlexTouch, Fiasp PenFill, NovoLog, NovoLog FlexPen, NovoLog PenFill)

From June 1, 2022, to May 31, 2023, these ten medications accounted for roughly 20% of overall expenses covered by Medicare Part D for prescription drugs, totaling approximately $50.5 billion.[4]

Additionally, the Centers for Medicare and Medicaid Services (CMS) will select up to 15 additional drugs for negotiation in 2027, up to 15 more in 2028 (including both Part B and Part D), and up to 20 more medications each subsequent year.[5]

Draft Guidance on the Medicare Drug Price Negotiation Program

On May 3, 2024, CMS issued draft guidance[6] that detailed the requirements and parameters for the second cycle of negotiations under the DPNP. This draft guidance also includes additional policies on how participating drug companies will make negotiated MFPs available in 2026 and 2027. Key topics covered in the draft guidance include[7]:

- Manufacturer-reported data and evidence related to alternative treatments should be considered when developing an initial offer to participating drug companies.
- CMS will consider patient-focused information on selected drugs while developing its initial offer
- The process and format are reported for the offer and counteroffer exchange between CMS and drug companies.
- The DPNP requires the exchange of data between dispensing entities (such as pharmacies) and participating drug companies. This exchange occurs via a Medicare Transaction Facilitator (MTF) and serves two purposes: facilitating access to MFPs for selected drugs by dispensing entities and providing claim-level data elements to primary manufacturers when a selected drug is dispensed to an MFP-eligible individual.
- CMS seeks input on options for MTF to offer a voluntary payment facilitation feature. This functionality would assist participating drug companies and dispensing entities in ensuring access to the MFP for eligible individuals.
- Participating drug companies must meet requirements to make the MFP available to MFP-eligible individuals and dispensing entities.

This draft guidance is open for a 60-day public comment until July 2, 2024. CMS anticipates issuing final guidance in the fall of 2024.

WHAT ARE THE IMPLICATIONS OF THE IRA ON RWE?

The drugs selected for inclusion in the IRA often serve multiple indications and treatment lines and may be used in combination with other medications. Unlike traditional health technology assessments (HTA), where real-world evidence (RWE) for an active therapy is typically lacking, assessments conducted under the IRA framework can utilize RWE for both the active treatment and its comparators. These comparators may be part of newer therapeutic strategies, including novel treatment sequences. Therefore, to establish additional benefits, it is essential to consider a comprehensive view of the indications, treatment lines, and formulations. RWE represents a promising avenue for achieving these goals.[1]

Manufacturers must provide evidence supporting efficacy, safety, unmet clinical needs, and impact on special populations during price negotiations. Epidemiological data, comparative effectiveness, health system burden, and subgroup analyses will significantly influence drug pricing and sales volume. These analyses can be enabled through fit-for-purpose real-world data (RWD). Suboptimal evidence management can put manufacturers at a competitive disadvantage.

While the initial phase of the DPNP unfolds, manufacturers can leverage RWE to highlight treatment value. RWE enables manufacturers to broaden their comparisons, including high-cost outcomes like hospitalization rates. Since most treatments on CMS' price negotiation list have been accessible for at least ten years, proving their effectiveness beyond clinical trials (and the original comparator) necessitates RWE. While patient experience and preferences play a vital role, administrative claims and electronic health records (EHR) do not fully capture these critical outcomes. To comprehensively assess the patient's experience, additional data sources like surveys, patient-reported outcomes, social media monitoring, patient-generated health data, and social determinants of health are essential.

Integrated evidence planning (IEP) can play a pivotal role in navigating some of the challenges of the IRA. IEP is a comprehensive process incorporating diverse types of data, scientific methods, and cross-functional expertise across a product's lifecycle to generate key evidence about a therapy's benefits, safety, and value.

ADVANCING RWE COLLECTION AND UTILIZATION UNDER THE IRA

In many health systems, price negotiation occurs at product launch. Under the IRA, the maximum fair price will be set after the drug has already been on the market for ten years or more. RWE is expected to play a pivotal role in demonstrating the drugs' realized value and outcomes for Medicare patients. During negotiation, extensive patient follow-up information will need to be available.

This will create a considerable demand for RWD collected alongside routine clinical practice.

Preparation will be critical, mainly due to the short 30-day window for manufacturers of the selected drugs and interested parties to submit data to CMS. Companies should determine how to prospectively plan data collection to support the future value case for their products. Transparency in data collection initiatives will be imperative to engender trust, include patients whose data will be used, and convince decision-makers of data integrity. Beyond consideration of product-specific data collection and RWE generation, companies must engage in broad stakeholder conversations to discuss the methods and practices in the collection and use of RWD. While there has been considerable progress in recent years, there is a long way to go before RWE practices and methods are fully refined and accepted. Implementation of the IRA can prove to be the catalyst.

COMPARATIVE EFFECTIVENESS RESEARCH AND RWE

While the precise impact of RWE on CMS drug price negotiations remains unclear, several methods like utilizing the target trial emulation (TTE) framework/causal inference, conducting quantitative bias analysis (QBA), and extrapolating outcomes from open-label extension data to estimate lifetime value can be helpful.[1] The CMS prioritizes RWE over quality-adjusted life years (QALYs) when assessing the value of treatments. Manufacturers

impacted by these changes should have access to extensive RWD accumulated over several years. However, the inflexibility of traditional analytics may make it challenging to meet deadlines. Manufacturers' proficiency in data analysis is crucial for handling quick turnarounds of RWE. To secure favorable negotiated prices, manufacturers need robust evidence highlighting how the treatment addresses an unmet medical need. Additionally, comparative effectiveness research is essential to demonstrate the treatment's value for specific sub-populations, especially those under-represented in initial clinical trials. These data analyses should highlight incremental improvements in both clinical and economic outcomes.

UTILITY OF CAUSAL INFERENCE METHODS IN THE CONTEXT OF THE IRA

Confounding is a key form of bias present in RWD that can be handled by causal inference. Causal inference is a more novel yet more robust approach for extracting causal effect from RWD. It considers the true causal structure of the problem; emulation of a target trial is natural with this approach & it uses totality of data. Target trial emulation (TTE) is an approach that applies the principles of randomized controlled trials (RCTs) to observational data. Instead of conducting a new RCT, TTE emulates a hypothetical RCT using existing observational data as the primary source. TTE is a two-step approach that requires the pre-specification of a target trial, which is then emulated in downstream analysis using appropriate causal inference methods. Enbrel (etanercept), a biologic tumor necrosis factor (TNF) blocker, is on the list of the initial ten drugs subject to price negotiation. Enbrel has received approval for multiple indications, including rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, plaque psoriasis, and ankylosing spondylitis.[8] It acts as a soluble receptor that binds to both TNF-alpha and TNF-beta and competes with other TNF blockers and various advanced therapeutic agents for managing these conditions.

Given the challenges of conducting large RCTs across all indications, researchers can use claims-linked EHR data to emulate target trials. This approach can assess long-term effectiveness and safety by comparing etanercept to other treatments.[9] While it may not be feasible to conduct causal inference studies for all drugs and all outcomes under CMS consideration, leveraging causal inference in claims-linked EHR can significantly expand the evidence base compared to relying solely on RCT data. The causal inference approach helps identify scenarios where RWE struggles to provide reliable comparative effect estimates, such as cases where emulating the target trial would require unreasonable assumptions. The causal estimation of treatments using RWD necessitates clinical equipoise, which may not always be present, especially when a single drug dominates as the primary treatment choice. By applying causal inference methods to large real-world databases, researchers can gain valuable insights into what these trials would have looked like and assess the comparative long-term benefits of multiple competing interventions.[1]

QUANTITATIVE BIAS ANALYSIS TO ADDRESS THE INHERENT LIMITATIONS OF RWD

RWD often presents inherent limitations, including substantial missing data, unrecorded variables, and inconsistent measurements. When applying the causal inference framework, these factors can significantly impact the validity of estimates. To tackle the inherent limitations of RWD, regulatory and payer bodies are increasingly advocating for the use of QBA as a potential remedy.[10] External bias adjustment has recently emerged as a promising QBA approach for addressing RWD limitations. This method involves incorporating external information, simulating potential biases, and adjusting the data accordingly. The adjustment can be performed using probabilistic sensitivity analysis within a Bayesian framework. However, external bias adjustment relies heavily on external data and clinical input, making it resource intensive.[9] Another approach within QBA for handling missing data in RWD involves a 'tipping point' analysis. This technique explores a broad spectrum of scenarios and is not influenced by subjective bias strength specifications before conducting the study. However, interpreting whether a tipping point is plausible can be challenging. An illustrative example of this approach is delta-adjusted pattern imputation.[11] In the context of IRA and price renegotiation, QBA can help address the inherent limitations of RWD. External adjustments and tipping-point analysis can aid in gauging a wide range of cost-benefit scenarios that would otherwise not have been possible with RWD and causal inference alone.

CONCLUSIONS

The IRA introduces price negotiations and evolving value requirements for drugs throughout their lifecycle. Drug manufacturers can adopt statistical methods like causal inference and QBA to overcome limitations in RWD. Integrating high-quality RWE into pricing negotiations will ensure effective and affordable treatments for Medicare patients. The methodological improvements in evidence generation can substantially impact healthcare policy and pricing strategies. This approach streamlines the negotiation process by optimizing therapeutic outcomes for Medicare beneficiaries and aligns with the broader objective of ensuring access to cost-effective, high-quality healthcare solutions. While significant policy changes can disrupt revenue streams, understanding the components of the Medicare DPNP and how RWD can shape the narrative is crucial for manufacturers. These capabilities are essential, regardless of whether treatments are part of the initial group impacted by the Medicare DPNP. Ultimately, nearly all major manufacturers will have treatments affected by this program. The IRA specifies the selection of increasingly larger groups for drugs in the future in Part D and later in Part B. The integrated approach to evidence generation, including RWE's pivotal role, is crucial for informed pricing discussions. By addressing inherent biases in RWE, these methodologies enhance the credibility of evidence for IRA negotiations.

Axtria's RWE, HEOR, and Evidence Synthesis team is a trusted partner in navigating this uncertainty. Axtria offers integrated evidence generation by leveraging a full spectrum of analytics (descriptive, diagnostic, predictive, and counterfactual) across the product lifecycle, encompassing pre-launch, launch, and post-launch activities. Axtria leverages advanced methods like causal inference and clinical trial simulations to synthesize RWE. Axtria is well-positioned to assist manufacturers in adapting to these changes, ensuring they are well-prepared for future negotiations and assessments of both currently licensed drugs and those in development.

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