A Framework for Re-Thinking Evidence Generation Requirements in the United States: It's Time to Meet Expectations of the Inflation Reduction Act

Poster RWD77

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Background

After the Inflation Reduction Act (IRA) was enacted in 2022, the Centers for Medicare and Medicaid Services (CMS) gained the authority to negotiate Part D drug prices with manufacturers.[1]

In August 2023, CMS announced the first ten drugs that would be subject to the Part D Medicare Drug Price Negotiation Program, which will be extended to Part B drugs in 2028.[2] In the first round, CMS selected 10 branded products including Januvia®, Farxiga®, Fiasp®/Novolog®, Enbrel®, Jardiance®, Stelara®, Xarelto®, Eliquis®, Entresto®, and Imbruvica® for price negotiations.[3]

Within the negotiation process, while determining a product maximum fair price (MFP), CMS will also evaluate comparative effectiveness data to better understand clinical benefits associated with specific treatments, in each instance, as compared with appropriate therapeutic alternatives. Therefore, CMS will work to establish pricing through integration of comparative effectiveness evidence and net prices of selected treatments and their alternatives.[4]

Per issued guidance around supporting evidence for the negotiation process, CMS will consider clinical trial data; real-world evidence (RWE); existing literature on unmet needs, comparative therapeutic efficacy and safety; and the impact of other treatments for the relevant disease, evaluating their role within the broader clinical context. Robust studies that include Medicare-eligible patient populations will be prioritized.[5]

The importance of randomized clinical trials (RCTs) is limited in negotiations because they were conducted in an idealized setting with only a limited patient population. RWE is an intuitive means to inform these price negotiations because each selected product has been on the market for sufficient time to accumulate real-world data over the 7 to 11 years following initial FDA approval. As real-world practice incorporates a relatively heterogenous and broad population with various uses of these products (vs. the highly selected and strictly controlled environments of the pivotal trials), comparative effectiveness based on RWE will represent a more realistic assessment of clinical practice and therefore serve as a particularly valuable component of the evidence package.[6]

Recent analyses have shown that the comparative RWE available for the first ten products subject to negotiation is notably limited.[5]

In this context, we focused on exploring guiding principles for the design and conduct of RWE studies that are expected to be a critical component of evidence considered for Medicare price negotiations.

Objectives

- To explore the role of real-world data (RWD) in Medicare Drug Price Negotiations, and determine if a framework based on a summarization of critical considerations could help inform generation of credible and meaningful RWE to inform pricing processes

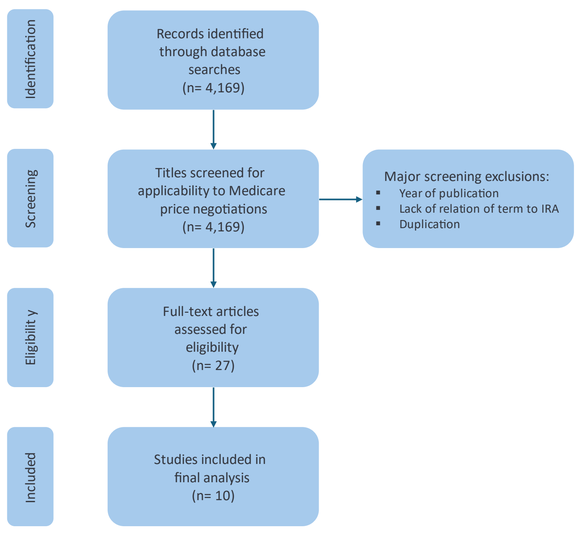
Methods

We conducted a literature review within Embase, PubMed, and relevant grey literature, limited to those published in English from September 2022 to September 2024 that included the terms "Inflation Reduction Act," "Real-world Evidence", "Coverage with Evidence" "health technology assessment", and/or "price negotiation"

Our search aimed to explore:

- Availability of RWE studies focused on Medicare enrollees, and how these studies have been used previously in the decision-making process for price negotiation;
- How CMS will set its initial price offer;
- If CMS has offered guidance on how RWE will be leveraged, and which are the related required standards for RWD.

Figure 1. PRISMA Chart



Results

Our review identified 4,169 relevant articles, of which 27 (0.6%) mandated full review; 10 (37.0% of all those selected for full review) had relevant information and were included in our review. In our search, we found out that out of 170 comparative effectiveness studies based on RWD, 55 (32.4%) used Medicare RWD and 34 (20.0%) commercial claims data that included information on patients covered by either Medicare Advantage or Medicare Supplementary.[7] Studies focused on apixaban and/or rivaroxaban accounted for most identified publications:[7]

- Several studies also were identified that examined the comparative effectiveness of etanercept
- Limited RWE on comparative effectiveness were identified for other treatments prioritized for CMS price negotiations.

To establish its initial price offer for Part D drugs selected for negotiation, CMS will calculate a "ceiling maximum fair price", which will be determined by either the net price faced by Part D payers or a percentage of the non-federal average manufacturer price, adjusted based on the duration of commercial availability of the drug:[8-9]

- For Part B drugs, maximum fair price will be based on average sales price or the same percentage, further adjusted using information from manufacturers concerning research and development costs, production and distribution expenses, federal subsidies, patents, and sales data
- CMS will not exceed this ceiling price in its offers. If no alternatives exist, CMS will use the Federal Supply Schedule or prices from the "Big Four," provided these do not exceed the ceiling price

Results Cont.

CMS will then evaluate clinical benefits of the selected drug, including efficacy/effectiveness, quality of life, safety, impact on the target population, and if the drug addresses unmet needs.

- While costs and outcomes will be considered as part of the evidence package, quality-adjusted life-years (QALYs) will not.
- Finally, CMS will consider any manufacturer specific factors to determine the initial fair price.

CMS has already highlighted the significance of RWE in its guidance, indicating that RWD will be utilized to help identify therapeutic alternatives and assess clinical benefits. Furthermore, CMS has emphasized that it will prioritize studies based on their methodological rigor. However, it has not clarified how RWE is considered within its evidence hierarchy, the standards used to evaluate methodological rigor, or if CMS will conduct its own RWE analyses to address evidence gaps in support of the negotiations.

In the process of refining the initial MFP, CMS will incorporate RWE, clinical data, expert reviews, and patient insights to fully assess the drug's comparative benefits, risks, and side effects. If manufacturers dispute the initial price offer, they must submit additional data to strengthen their counteroffers. Additionally, CMS plans to hold patient-centered listening sessions, where input from patients, caregivers, and advocacy groups will be gathered on alternative therapies and relevant considerations for the drug's evaluation.[10]

Discussion

Our review highlighted that there is still uncertainty on the use and impact of RWE studies in the CMS pricing negotiations.

RWE is an important source of information for CMS's price negotiations, as it can accumulate over the 7 to 11 years following FDA approval and subsequent commercial launch. By the time negotiations occur, data from RCTs will be outdated or irrelevant, particularly because RCTs comprise relatively homogenous and highly selected populations who receive therapy under tightly controlled environments, which are not readily generalizable to the real-world clinical experience of Medicare beneficiaries. Therefore, timely real-world comparative effectiveness data is essential.

However, it is important to recognize that "not all RWE is created equal", and a priori agreement on a number of factors related to selection of appropriate RWD and means to conduct (comparative) effectiveness assessments is vital to ensuring fair and robust assessments are conducted. Such a framework should include the following:

- The means to identify "fit-for-purpose" RWD, which should incorporate relevant patient populations, exposures (including evidence of use of the medication[s] in question), outcomes (limiting to those that are clinically relevant and that can be assessed confidently in the identified data source), and covariates (required to control for channeling/selection bias and other sources of confounding)
- Clearly specified and defined study measures, including exposures, outcomes, and covariates. Operational definitions should be based on knowledge of the selected RWD source(s), including overcoming potential limitations of the data (e.g., use of multiple outpatient claims with relevant diagnoses over some period of time to account for errors of omission/commission and/or the possibility of use of "rule out" codes)
- Clearly specified and defined analytic approach, including the means by which cohorts will be balanced (in instances of comparative effectiveness) and the possibility for sensitivity analyses to account for uncertainty in operational definitions inherent in RWD. For example, if sample selection processes include multiple encounters with specified diagnoses/procedures/therapies, sensitivity analyses may examine the impact of varying sample selection on outcomes of interest. Such analyses are important in instances of RWE generation—especially when selected measures cannot be defined with certainty in the selected source(s)
- A priori agreement on the definition of system/patient impact. For example, if comparative effectiveness is defined as a reduction in hospitalizations (or a corresponding decrease in total healthcare costs associated with admissions to CMS), this outcome should be specified—and agreed upon between CMS and the manufacturer—before analyses commence
- The means by which residual bias will be assessed/quantified. While advanced statistical methods are available to balance cohorts in advance of comparative effectiveness assessments, they are only as good as the measures that can be constituted to support them. Accordingly, quantitative bias assessments following "full analyses" should be undertaken to better understand the degree to which results may be explained by reasons other than exposure (e.g., residual confounding).

Both manufacturers and CMS should pursue the generation of high-quality comparative real-world evidence studies within the Medicare population to ensure that price negotiations are grounded in solid evidence.

Conclusions

While RCTs are vital to assess efficacy and safety of medications, they are insufficient to inform their performance in clinical practice, for which RWD is required. Given the importance of the resulting RWE to inform drug pricing and value decisions, a framework is required to inform methodological standards for what "good RWE" looks like, and how it can be used to inform mandated price negotiations. We propose such a framework that requires an assessment of available sources, pre-specification of all study measures and operational measures, and a full consideration of variability based on vagaries inherent in RWD on the findings through sensitivity analyses and residual bias assessment. We believe it vital that manufacturers and CMS use such a framework to ensure rigorous and robust RWE can be generated from fit-for-purpose RWD to meet relevance evidence needs and standards, and to help inform MFP negotiations.

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