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Use of real-world evidence in the Medicare Drug Price Negotiation Program: A checklist for the Centers for Medicare and Medicaid Services and manufacturers

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Abstract

Under the Inflation Reduction Act's (IRA's) - Medicare Drug Price Negotiation Program, the Centers for Medicare & Medicaid Services' (CMS's) "maximum fair price" must be informed by evidence on factors such as therapeutic advance of the selected drug compared with its alternative, comparative effectiveness across clinical and patient-reported outcomes, the impact on specific populations, and the ability to address unmet medical needs. This paper describes how real-world evidence could improve CMS decision-making and creates a best practices checklist to help CMS evaluate the quality of any manufacturer-submitted evidence. The checklist was developed in four steps: (i) identification of the IRA requirements for determining the maximum fair price through a review of official guidance from CMS, (ii) assessment of provisions that could be supported by real-world evidence (RWE) in addition to clinical trial evidence, (iii) literature review on existing best-practice guidelines relevant to RWE, and (iv) consolidation of these RWE guidelines into a checklist through a series of web conference discussions among experts. The checklist aims to improve the quality of the information available to CMS during the drug price negotiation process.

Lay Summaries

Under the Inflation Reduction Act's Medicare Drug Price Negotiation Program, the Centers for Medicare & Medicaid Services (CMS) will set a "maximum fair price" for certain drugs. To determine this price, CMS considers various factors, such as how well the drug works compared with alternatives medically and in patient experiences, its effectiveness for different groups of people, and how it addresses health needs that have not been addressed.

This paper explores how using real-world evidence—defined as data from everyday healthcare settings—could help CMS make better-informed decisions. It also presents a practical checklist to help CMS assess the quality of this evidence provided by drug manufacturers. The checklist was created through a four-step process: (1) Reviewing CMS guidelines to understand what they need to set prices; (2) Identifying where data from everyday healthcare settings can support these decisions alongside clinical trial results; (3) Examining existing best-practice guidelines for using real-world evidence; (4) Bringing together experts to refine these guidelines into a clear, helpful checklist. The goal of the checklist is to ensure CMS has reliable, high-quality information when negotiating drug prices, ultimately benefiting patients and the healthcare system.

Key words: real-world evidence; real-world data; Inflation Reduction Act; best practices; guidelines; Medicare; drug price negotiation; maximum fair price.

Key Takeaways

- Given that IRA price negotiations occur 9-13 years post-drug launch, real-world evidence (RWE) may offer valuable insights to inform decision-making by the Centers for Medicare & Medicaid Services (CMS). To fully harness this potential, however, CMS must adopt standardized methodologies to assess the quality and reliability of RWE.

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- A best-practice checklist, rooted in existing guidance, was developed to provide CMS with a rigorous, transparent tool for evaluating submitted studies. The framework developed in this article not only ensures alignment with IRA requirements but also supports drug manufacturers in generating high-quality, methodologically sound evidence.
- Explicit guidance from CMS on RWE standards and evaluation criteria is critical for consistency and transparency. By defining expectations, CMS can enable manufacturers to design studies that better address regulatory priorities, ultimately enhancing the relevance and quality of evidence in drug price negotiations.

Introduction

With the passage of the Inflation Reduction Act (IRA), the federal government can now "negotiate" prices directly with drug manufacturers for certain high-cost, sole-source drugs.[1,2] The law states that the Centers for Medicare and Medicaid Services (CMS) will negotiate a "maximum fair price" (MFP) for high-cost Medicare Part B and Part D drugs that have been on the market for ≥9 years (or ≥13 years for biologics).[3] Under the Medicare Drug Price Negotiation Program ("Negotiation Program"), CMS will evaluate evidence related to therapeutic advance of the selected drug against its therapeutic alternative, comparative effectiveness across clinical and patient-centered outcomes (PCOs), impact on specific populations, and ability to address unmet medical needs. However, the guidance lacks clarity on specifically how CMS will effectively identify this information.[3] While clinical trials are a key evidence pillar, trials have limited follow-up times, inadequate sample sizes for analyzing subgroup effects, among other limitations.[4] Moreover, trial participants may not represent real-world Medicare beneficiaries due to strict inclusion/exclusion criteria, which may exclude patients with co-morbidities common among the elderly.[5]

Due to these limitations, CMS has been willing to incorporate real-world evidence (RWE) in the MFP negotiation process but has not yet offered guidance on what types of RWE would be eligible for consideration. Real-world evidence is defined as the clinical evidence regarding the usage and potential benefits or risks of a drug derived from analyzing real-world data (RWD) collected from routine healthcare delivery.[6] RWE overcomes some limitations of clinical trials by assessing a treatment's performance in actual clinical settings and over longer follow-up periods than in randomized controlled trials (RCTs). As negotiations occur 9-13 years post-launch, RWE is likely to be substantial, enabling CMS to access up-to-date evidence on the treatment's value and therapeutic alternatives.

In January 2025, CMS released draft guidance on developing RWD for factors used in national coverage determinations.[7] Similarly, RWE offers a unique opportunity to inform MFP negotiations and CMS needs to provide clear guidelines to drug manufacturers on how best to generate RWE. Accordingly, this paper (i) demonstrates why the use of RWE would improve CMS decision-making and (ii) creates a best practices checklist for manufacturers to plan and for CMS to evaluate RWE studies.

Why RWE is needed to comply with the IRA price negotiation provisions

IRA legislation and CMS's guidance states that it will set drug prices based on not only cost, but also evidence on selected drugs relative to therapeutic alternatives over six dimensions: (i) identification of therapeutic alternatives, (ii) determination of therapeutic advance (health), (iii) determination of therapeutic advance (costs/resource use), (iv) impact on "specific populations," (v) measurement of PCOs, and (vi) assessment of ability to address unmet medical needs.[3] While IRA does not mandate the type of information CMS should use to evaluate drugs based on these criteria, RWD could lead to better decision-making across each of these (Table S1).

Identification of therapeutic alternatives

CMS must identify an appropriate therapeutic alternative for comparison to assess the selected drug's performance. The control arm of RCTs conducted prior to the Food and Drug Administration (FDA) approval is an obvious choice,[8,9] but RCTs may not reflect current standards of care (SoC) due to evolving treatment patterns and innovations since the drug's launch.[10-14] For instance, treatment for multiple myeloma evolved from dexamethasone to bortezomib or lenalidomide monotherapy to eventually a series of different combination therapies.[15] RWE can also supplement clinical guidelines by capturing to what extent SoC has changed over time in the real world and whether specific therapies are more likely to be used for Medicare beneficiaries. Expert opinion is useful, but these experts often reside at leading academic medical centers; RWE can complement these experts by determining how frequently expert-recommended alternatives are being prescribed in non-academic, community practices.

Evaluation of therapeutic advances (health)

CMS is mandated to evaluate evidence regarding the selected drug's relative therapeutic advance in health outcomes. While RCTs assess comparative clinical benefits, they may not reflect a drug's effectiveness in real-world settings due to efficacy-effectiveness gaps or changing SoC.[16-20] For instance, long-acting injectable antipsychotics used to treat patients with schizophrenia may have similar efficacy—as observed in clinical trials—to oral treatments[18]; however, RWE has identified their superior effectiveness due to their less frequent dosing resulting in improved medication adherence.[19]

The RCT-DUPLICATE initiative shows that well-designed RWE studies have reliable conclusions. Specifically, studies closely emulating RCT designs with replicable inclusion/exclusion criteria and a readily-identifiable "time zero" generally reached similar conclusions to RCTs.[21] However, poorly designed and executed RWE studies can produce unreliable results, underscoring the need for clearly defined quality standards.[22,23]

Evaluation of therapeutic advances (costs and resource use)

While CMS is mandated to evaluate the selected drug's economic cost and resource utilization against its therapeutic alternatives, this information is rarely included in RCTs.

Conversely, some RWE (e.g., claims data) can readily measure the impact of pharmaceuticals use on total cost of care and specific types of healthcare utilization. The Congressional Budget Office, for instance, used RWE to estimate that a 1% decrease in prescriptions filled by Medicare beneficiaries would cause Medicare's spending on medical services to increase by roughly 0.20% due to cost offsets from prescription drug use.[24]

Effect on "specific populations"

CMS's effort to assess a drug's impact on health outcomes for specific populations—including individuals with disabilities, the elderly, terminally ill patients, and children—is limited by the fact that these populations are underrepresented—or often entirely excluded—from clinical trial populations.[25,26] Nearly 50% of RCTs used age and the presence of various comorbidities as exclusion criteria.[27] Even when these subpopulations are included, trial sample sizes may be too small to accurately measure subgroup-specific treatment efficacy.[28,29] Conversely, RWE often contains much larger, more representative samples, enabling CMS to better understand a treatment's impact on IRA-mandated specific populations.

Consideration of PCOs

CMS guidance states it will consider PCOs when assessing a treatment's clinical benefit, but RCT data on these is often limited. For instance, only about two-thirds of lung cancer RCTs[30] and half of heart failure RCTs included PCOs, with overall modest reporting quality.[31] Real-world registries collecting PCO data longitudinally or patient preferences surveys can be invaluable to identify unmet need and a treatment's impact on the patient's own experience. For instance, there are well-established registries in oncology (Surveillance, Epidemiology, and End Results), immunology (FORWARD), and organ transplantation (Scientific Registry of Transplant Recipients) to name just a few. CMS and manufacturers can rely on already-validated PCOs such as Patient-Reported Outcomes Measurement Information System (PROMIS), the Medicare Health Outcomes Survey (HOS), and FOTO Patient Outcomes, among others.[32]

Assessing ability to address unmet medical needs

RWE can help assess whether a drug addresses unmet need. FDA defines unmet need as "…a condition whose treatment or diagnosis is not addressed adequately by available therapy" and requires "an immediate need for a defined population…or a longer-term need for society."[33] For instance, RWE can identify unmet needs from decreased adherence or discontinuation due to toxicity, burdensome modes of administration, or suboptimal treatment response.[34,35] If no therapy is available, manufacturers can use historical health outcomes data to show the magnitude and specific manifestation of the unmet need and burden of illness (e.g., poor quality of life (QoL) [registries], higher hospitalization rates [claims], increased antibiotic resistance [electronic health records/EHR]).

Limitations of RWE

Despite its benefits, RWE has limitations. First, real-world settings lack RCTs' controlled environment, and patients who are more (or less) ill may receive newer treatments, potentially resulting in the estimated effectiveness being biased downwards (upwards).[36-38] Second, RWE studies may not always be nationally representative, though this is typically less problematic than with RCTs. Third, RWD—including EHR, claims, or registries—may be incomplete or inconsistent.[36-39] Finally, adjusting for confounders in observational studies (e.g., propensity score matching) are complex to implement statistically.[36,39-41]

To ensure that any RWE study that CMS may consider addresses these limitations, the authors created a checklist to help manufacturers conduct high-quality RWE studies and guide CMS in evaluating their rigor and relevance for MFP negotiations.

RWE best practices and guidelines checklist

To enable CMS to confidently use RWE as part of negotiations, a draft Negotiation Program RWE Checklist was created (Table 1). It was built from and references existing guidance and serves as a tool for manufacturers to follow established best-practice frameworks and incorporate CMS's requirements. The checklist was also designed for easy adaptation into CMS's existing Negotiation Data Elements Information Collection Request (ICR) forms, enabling manufacturers to present key IRA-related evidence without unduly burdening CMS review.

The checklist helps both CMS and drug manufacturers:

- **Quality standardization for CMS:** The checklist provides a structured framework for CMS to systematically evaluate submitted RWE based on the six dimensions mandated by the IRA and ensures that the evidence aligns with CMS's evaluation criteria. It also increases the transparency of the RWE evaluation process.
- **Guidance for manufacturers:** The checklist provides clear guidelines for generating high-quality RWE, ensuring that manufacturers follow best practices, ensuring transparency, replicability, and methodological rigor for any evidence to be submitted to CMS as part of negotiations. It also allows manufacturers to plan in advance of how best to collect RWE for drugs likely to undergo MFP negotiation.

This checklist was developed in four steps. First, mandated provisions from the IRA for determining MFP were identified through a review of official guidance from CMS. Second, provisions that could be informed by RWE were identified. Third, a targeted literature search identified existing best-practice methodological guidelines relevant to RWD use and RWE reporting (Table S2). Fourth, the best-practice guidelines were consolidated into a checklist through discussions with the co-authors. To ensure all stakeholder perspectives were incorporated, the co-authors had diverse backgrounds, including expertise from the perspective of academia (Bharmal, Shafrin, Tunis, Whittington), government (Shafrin, Than, Tunis), health technology assessment (Tunis, Whittington) pharmaceutical manufacturers (Bharmal, Willke), and non-profit organizations dedicated to value assessment (Shafrin, Whittington, Willke; Table S3).

The checklist asks manufacturers to report key metrics that should be considered in RWE studies to ensure high relevance and quality:

1. **Relevance of evidence.** State and describe how the study is relevant to IRA provisions (including how the RWE

Table 1. Real-world evidence checklist for CMS for Medicare Drug Price Negotiation Program.

Instructions: The checklist is to be submitted as part of the visual representations to support responses in the CMS Negotiation Data Elements ICR Form Section I, Questions 30-62.

Category	Item	Details for Centers for Medicare and Medicaid Services (CMS)							Notes
Relevance of Evidence	**Which IRA Provision is your RWE study addressing?** *[Select all that apply]*	Identifying Therapeutic Alternatives ☐	Considering Therapeutic Advances (Health) ☐	Considering Therapeutic Advances (Costs and Resource Use) ☐	Examining Impact on "Specific Populations" ☐	Considering Patient-Centered Outcomes ☐	Assessing Ability to Address Unmet Medical Needs ☐	Other (provide details in "Notes") ☐	
	Applicable question group in CMS Negotiation Data Elements ICR Form *[Select all that apply]*	Manufacturer-Focused Inputs ☐	Patient- or Caregiver-Focused Inputs ☐		Clinical-Focused Inputs ☐	Health Research-Focused Inputs ☐	Other Public Inputs ☐		
	Question Number(s)								
	Summary of Study Findings *[Provide description]*								
	How should these results impact MFP? *[Provide description]*								
	How do these RWE results add to existing information (i.e., in clinical trials)? *[Provide description]*								
Study Design and Reporting	**Research Question**								
	PICOTS *[Describe study population, intervention, comparator, outcomes, timing, and setting]*								
	Best Practice Reporting Guideline Used *[Select and upload guideline checklist as attachment]*	STaRT-RWE ☐	HARPER ☐	RECORD-PE ☐	ESMO-GROW ☐	CDA RWE Checklist ☐	ISPOR CHEERS ☐	Other (provide details in "Notes") ☐	
Study Quality	**What type of real-world data did your study use?** *[Select all that apply]*	Electronic Health Records (EHR) ☐	Claims Data ☐	Patient Registries ☐	Retrospective Chart Review ☐	Other Observational Cohort Data ☐	Other (provide details in "Notes") ☐		
	Briefly explain why the data source(s) are fit-for-purpose to address the study question								
	Best Practice Methods Guidelines Used *[Select and upload DataSAT checklist as attachment]*	SUITABILITY Checklist (for EHR) ☐	FDA Guidance (for EHR and Claims Data) ☐	FDA Guidance (for Registries) ☐	Other (provide details in "Notes") ☐				
	How did your study address potential biases of RWE? *[Provide description]*								
Study Validation	**Form of RWE Validation**	Peer Review Journal Publication ☐	Presented at Academic Conference ☐	Abstract Only ☐	Other (provide details in "Notes") ☐				
Incorporation of RWE [CMS Use Only]	**Should CMS include this evidence as part of determining the maximum fair price?**	Yes ☐			No (provide rationale in "Notes") ☐				
	How did CMS incorporate this RWE into the MFP determination?								

supplement clinical trial data), reference applicable questions in the ICR, and justify consideration in determining the MFP.
2. **Study design and reporting.** Describe the study design and reference best-practice guidelines for RWE reporting (e.g., HARmonized Protocol Template to Enhance Reproducibility [HARPER] guidelines[42]) (Table S2).
3. **Study quality.** List the best practices data guidelines used (e.g., FDA Guidance for EHR and claims data[43]), potential biases (Table S4), and describe the extent to which the study is susceptible to each bias and how they were addressed.
4. **Study validation.** Describe validation of the study (e.g., publishing in a peer-reviewed journal to ensure credibility, or presenting at academic conferences, or submitting an abstract to allow for expert feedback and dissemination, considering lengthy peer-review processes).

Discussion

With the advent of the IRA Negotiation Program, CMS is mandated to consider evidence surrounding a selected drug's performance relative to therapeutic alternatives. While RCT data have traditionally informed drug evaluations, RWE is uniquely positioned to capture data beyond efficacy, such as identifying real-world standards of care, measuring long-term effectiveness and safety, quantifying treatment impacts on total cost of care and resource use, determining a treatment's impact on subpopulations and PCOs, and identifying potential unmet needs. Despite the growing use of RWE from professional organizations globally,[44] study quality can be inconsisent.[45,46] While we recommend CMS conduct its own RWE studies, short timelines between drugs identification and price release may limit CMS's ability to conduct high-quality RWE studies for each drug on the list.

The checklist developed in this manuscript aims to provide greater clarity for CMS, manufacturers and academics about what RWE study features are necessary to be deemed of sufficient quality for informing the Medicare Drug Price Negotiation process. RWE quality could be further enhanced should CMS reduce the 2-3 year lag in releasing Medicare claims data.[47] The checklist is not only intended to help CMS evaluate study quality, but it also informs drug manufacturers and other stakeholders on the data sources and study designs likely to meet the quality standards for CMS to consider RWE within the MFP negotiation. Moreover, the Negotiation Program RWE Checklist aims to enhance transparency across all stakeholders. By building on existing RWE frameworks and best-practice guidelines, this checklist serves the goal of ensuring that CMS is presented with the best evidence possible to make informed decisions around IRA's MFP Negotiation process. Regardless of whether CMS adopts this checklist in its current form, clear guidance from CMS will significantly influence investments in RWD development for products that may be years away from entering MFP negotiations.

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Supplementary material

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Conflicts of interest

S.R.T. is a Principal with Rubix Health LLC, which received honorarium from FTI Consulting, as well as grants, fees, or other support from Arnold Ventures, Lumanity, and Bellberry Ltd., Australia, for unrelated work. J.S. and K.T. are employed by FTI Consulting, which received funding from AstraZeneca United States for the research used to develop the RWE checklist. M.D.W. has received grants or contracts from the National Pharmaceutical Council, No Patient Left Behind, Institute for Clinical and Economic Review, and Lumanity for unrelated work. R.J.W. was formerly employed by Pfizer, and has received consulting fees from ISPOR, Viatris, and Covia Health Solutions for unrelated work. M.B. is employed by AstraZeneca United States, which provided funding for this research.

Please see ICMJE form(s) for author conflicts of interest. These have been provided as supplementary materials.

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