



Understanding the Context, Selecting the Standards:

A Framework to Guide the Optimal Development and Use of Real World Evidence for Coverage and Formulary Decisions

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Introduction

It is now widely acknowledged that real world evidence (RWE) – evidence derived from the analysis of data collected either prospectively or retrospectively from observations of routine clinical practice – is transforming the process through which health care payers make coverage and formulary decisions for pharmaceuticals.¹ Increasingly, efforts to design the standards for prospective RWE analyses have convened manufacturers, payers, and patient groups to ensure that evidence generated is both rigorous and fully informed by what matters most to patients.²⁻⁴

Both payers and manufacturers perform analyses of RWE, with wide variation in the scope and sophistication of their efforts. But current thinking about the use of RWE for coverage and formulary decisions is often still dominated by one picture: that of a manufacturer, who has purchased an aggregated dataset on which they have performed multiple analyses, coming to a payer to share results that shine favorably upon the manufacturer's product. This scenario is often implicit in the numerous white papers that have addressed the barriers to the use of RWE by payers, or that have outlined best practices in the methods of observational analysis in order to create more transparency and generate more trust in the results of manufacturer-driven analyses.⁵⁻⁷

This paper presents a new conceptual framework to address three elements largely missing from these earlier efforts focused on defining “best practices” or “standards” for RWE: 1) how to understand the role that contextual factors play in determining how high the evidentiary standard, or “bar” will be in each situation; 2) how to tailor key process and methodological approaches to

the height of that evidentiary bar; and 3) how to ensure that broader process principles that support transparency are integrated successfully throughout the course of any RWE initiative. This paper is a companion piece to a detailed background paper on the use of RWE in coverage decisions developed for the Institute for Clinical and Economic Review (ICER) Policy Summit held in December 2017. The insights and recommendations presented here arose from the discussion among a broad set of payers and manufacturers participating in that meeting, and do not represent a formal consensus of opinion among these stakeholders. But all participants would agree that in the interactions among payers and manufacturers there resides some level of suspicion that analysis using observational data, despite its acknowledged ability to fill critical gaps in understanding about effectiveness and value, is less reliable and more open to manipulation than data from a randomized trial. This paper will therefore provide a framework and specific steps to help both manufacturers and payers meet the challenge of developing observational RWE through a transparent process that can be considered credible by all stakeholders.

The Framework

Discussion at the ICER Policy Summit discussion helped delineate a conceptual framework to support active collaboration between manufacturers, payers and other relevant stakeholders in the development, evaluation, and application of RWE in coverage and formulary decisions. The Framework is shown in Figure 1 below, and its specific elements described thereafter.

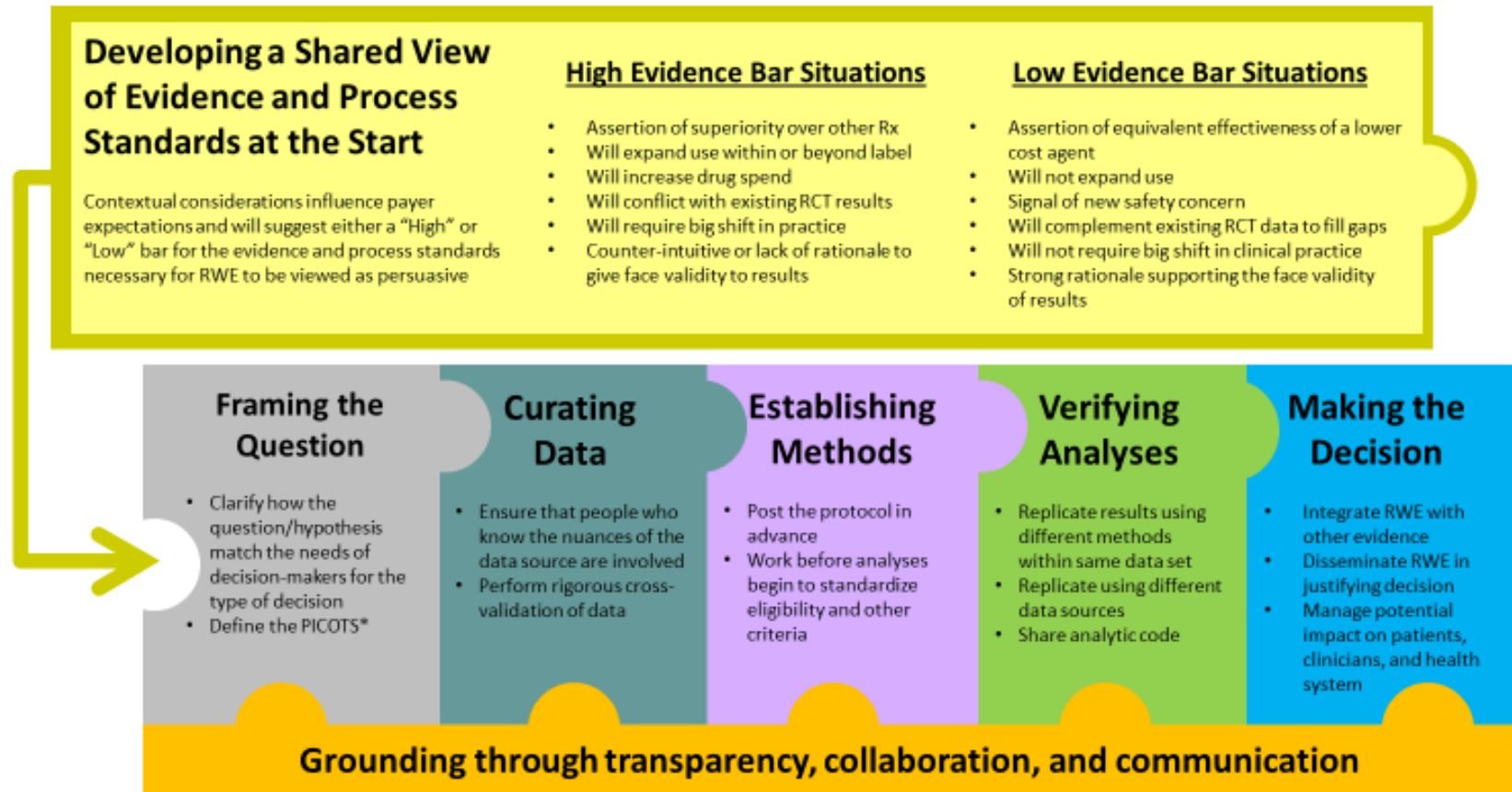
Overview

To support communication and active collaboration on RWE, payers and manufacturers need a clear understanding of the various steps within the process of developing and using RWE -

from framing the question, to making the policy decision – that can be taken to increase the validity of the analysis and ensure optimal application to coverage and formulary decisions. Many of these specific steps are well known and are discussed in greater detail in the companion ICER background paper on RWE. They range from measures to ensure data integrity, to ways to increase the transparency of analytic protocols, to mechanisms for testing the validity of the results. When these standards for producing high-quality RWE are ignored, the evidence will be at high risk of being incomplete, clouded by confounding variables, and ultimately misleading. But meeting the most rigorous form of every one of the standards that have been proposed for RWE takes substantial time and resources, creating a barrier that by itself can stymie efforts to develop and use RWE.

Therefore, in addition to a shared understanding of the steps involved in developing and using RWE, there is a need at the outset of any RWE effort to select the evidence standards that will need to be adopted for each step in the RWE process, in the light of the type of evidentiary assertion that the RWE is intended to support and the context surrounding the policy decision to be made. Only then can the right balance be struck between rigor and feasibility to produce RWE that will be persuasive in coverage and formulary policy.

Figure 1. Conceptual Framework to Guide Optimal Development and Use of Real World Evidence for Coverage and Formulary Decisions



*PICOTS: Patients, Intervention, Comparators, Outcomes, Time Horizon, Setting

Step 1: Developing a Shared View of Evidence and Process Standards

Before beginning a RWE analysis, the prospective research protocol should identify key contextual considerations to determine the evidence level and the corresponding methodological and process standards that should be followed. In some ways this can be associated with understanding the level of skepticism that will meet the results of RWE and selecting more rigorous standards when skepticism is likely to be high. But the contextual considerations that need to be addressed are much broader than skepticism arising from statistical concerns about sample size or confounding variables. They begin with the type of evidentiary assertion that the RWE is intended to make. As shown in Figure 1, evidentiary assertions to be made by RWE for coverage and formulary policy will generally be either one of superiority for a particular drug in comparison to others, or an assertion of the equivalent effectiveness of a lower-cost agent among two or more drugs. An intended assertion of superiority is one indicator that payers will require a relatively high evidentiary bar – a high level of rigor in evidence and process standards – in order to overcome concerns about the validity of RWE findings.

Other contextual considerations that suggest a high evidentiary bar include RWE use to inform coverage or formulary decisions that would expand use of a drug and increase cost. Assertions that a more expensive drug would lead to lower overall costs across the health system may not be quite as difficult to justify with RWE analyses as assertions of superior health outcomes, but will still require evidence standards that meet a high bar if they are to convince many payers. In addition, RWE that suggests the need for substantial changes to clinical practice, that conflicts with findings from randomized controlled trials (RCTs), or that lacks a clear underlying rationale (a biomedical explanation for the results) will also require stringent efforts to assure its validity. When seeking to use RWE to assert superiority, it may ultimately be wise to consider whether any RWE

program of observational studies can achieve the degree of trustworthiness required. When the bar for evidence and process standards is agreed to be very high, manufacturers and payers may consider pragmatic clinical trials (PCTs) to be a potentially better option than observational RWE, notwithstanding the current challenges to conducting PCTs.

In contrast, a relatively low evidentiary bar is often satisfactory when the intended assertion will be that a lower-cost drug offers equal effectiveness in real-world settings when compared to more expensive options. Similarly, a lower bar can often be adequate when the assertion supported by RWE will not expand use of current treatments or require a large shift in clinical practice, when there is a strong underlying rationale behind the findings, such as equivalent outcomes for drugs with similar mechanisms of action, and when the findings complement existing RCT data to fill obvious gaps in knowledge (e.g. use in a population group not included in the RCTs). RWE findings from analyses with lower evidentiary standards are also generally more readily accepted if they signal a new safety concern, since payers are risk-averse and wish to take early steps to minimize potential harms to patients.

The essential role these contextual considerations play in determining the evidentiary bar for acceptance of RWE, and thus the level of standards within each of the steps of RWE development, cannot be overstated. Both payers and manufacturers planning RWE efforts need address them before beginning any data analyses. Since payers will be assessing the credibility of manufacturer's RWE when making coverage or formulary decisions, it is particularly important for manufacturers to understand how much scrutiny payers will focus on the data and methods. This is why active engagement between manufacturers and payers before a manufacturer-led RWE effort commences can be so valuable. Whenever feasible, manufacturers should reach out to payers to

develop a shared view of the data, evidence, and process standards that can best meet the evidentiary bar for the specific analysis they plan to undertake.

It is also helpful for manufacturers to gain an understanding of the broader perspective payers have on evidence for coverage and formulary decision-making. Payers know that head-to-head trials of drugs are uncommon, and that RWE can be useful in examining drug classes where there are multiple competitors. But the general experience of payers is that when outcomes from drug treatment are evaluated through their own analysis, drugs often do not perform as well in clinical practice as they did in clinical trials. This is why using RWE to claim the contrary is likely to be viewed with skepticism.

It is important to understand that payers greatly value the perceived validity of RCT results and have put great reliance in the FDA's requirements for RCT evidence to justify new treatment approvals. Payers understand RCTs can be flawed, and often fail to address comparative effectiveness, longer-term durability of effects, or patient and clinician acceptability. Nonetheless, payers are hesitant to adopt an approach to the use of RWE that could threaten to undermine the incentives for manufacturers to conduct RCTs. RWE is viewed favorably as a complement to RCTs, a useful tool to fill in gaps in the evidence base, but deep commitment to RCTs remains. Manufacturers should be mindful of these views when approaching payers to discuss the contextual considerations relevant to their proposed generation of RWE.

Developing RWE: Framing the Question

Once the level of evidence standards and process have been clarified, decisions can be tailored to meet these standards within each step of RWE development and use. As shown in Figure 1, the first step in this chain is to frame the question and hypotheses to match the intended

evidentiary assertion. This may seem like a simple step, but it requires attention to the entire downstream RWE process. Only if the research question can be linked with an adequately curated data set, with clear methods, and with stipulated procedures for verifying the analyses, will the RWE have a chance of meeting the evidentiary bar and being fit for informing the policy decisions to be made. As mentioned earlier, it is at this stage that the RWE developers, whether they are manufacturers or payers, need to consider whether an observational study to generate RWE will be able to meet the evidentiary bar for the decision, or whether an RCT or PCT will be necessary instead. Manufacturers may find it useful to have discussions about the needed evidence and process standards and discuss proposed RWE research questions with multiple payers to make sure that the RWE effort will be accepted by a broad set of organizations. To make these discussions as tangible as possible, it is helpful to delineate the specific PICOTS for the analysis (Patients, Intervention(s), Comparator(s), Outcomes, Time Horizon, Setting). Describing the PICOTS for an analysis serves as a useful technique for ensuring that everyone fully understands the scope and intent of the overall analysis at a granular level that can help avoid later misunderstandings.

Developing RWE: Curating the Data

When efforts to generate RWE are planned prospectively, data sources and definitions for eligibility and key outcomes can be addressed in a collaborative fashion to maximize the transparency and reliability of the data. However, most RWE analyses are planned and performed using data previously gathered through routine mechanisms. Understanding and curating the data source is therefore a critical part of enhancing the trustworthiness of a retrospective RWE study. A key point here, particularly important when there is a high evidentiary bar, is to ensure that individuals who know the nuances of the data source are involved with the analyses from the earliest stages. Each data set has quirks, biases, and potential variations that could lead to

unknown errors in defining eligible patients, the interventions or comparators of interest, and the outcome measures being used. For example, drug utilization patterns and patient behaviors are heavily influenced by benefit design and drug coverage policies enforced by the payer; any RWE that evaluates cost needs to account for these factors as the results may be different in another data set with different preferred agents and benefit designs. Without expertise in that specific database the problems can be very hard to spot. This is one of the reasons why some payers are more likely to believe their own data rather than analyses using other data sets, even data from well-respected data vendors. The higher the evidentiary bar is for the overall RWE analysis; the more attention should be given to curating the data source in a way that meets agreed upon standards.

Developing RWE: Establishing Methods

As noted in the main body of the ICER Policy Summit background paper, there have been numerous multi-disciplinary efforts to outline the key approaches through which the analytic methods of RWE can address the perceived limitations of observational data analyses. These specific approaches include sophisticated propensity score matching and other ways to reduce the likelihood of unknown confounders distorting the results. The main point here is that, as with the other elements of RWE development, there are basic methodologic requirements that should be core to any RWE analysis, but additional focus and effort will be required when there is a higher evidentiary bar. Steps that can be taken to heighten the transparency or rigor of the methodology include: 1) the engagement of outside academic experts; 2) posting of the analytic protocol at clinicaltrials.gov in advance of any work; and 3) very careful attention to all eligibility and outcome

definitions, which, as mentioned earlier, should be woven into the curation of the data source and must involve individuals deeply knowledgeable of the source data.

One example of the importance of definitions, and of the risks presented by a lack of standardization, is shown by measures of adherence or persistence in use, which can be calculated using multiple methods.⁸⁻¹⁰ Both manufacturers and payers should seek to develop and use standard definitions for these and other metrics. Any deviation from these definitions should then be accompanied by transparent justification. Although standardization of key real-world outcome measures such as adherence is not currently the responsibility of any single organization, the Pharmacy Quality Alliance (PQA), International Society for Pharmacoeconomics and Outcomes Research (ISPOR), and the Academy of Managed Care Pharmacy (AMCP) are potential leaders in this area. As ICER welcomes RWE as part of its review process, it may also come to play a role in developing and communicating clear definitions for certain key outcomes.

Developing RWE: Verifying Analyses

Among the different steps in RWE development, mechanisms to verify analyses offer perhaps the broadest set of choices from which to select a tailored approach to match the evidentiary bar. For many payers verification is the most critical step in assessing the credibility of RWE for informing coverage and formulary decisions. Verification options include efforts to replicate results using different methods within the same data set, or trying to replicate the results using the same methods applied to a different data source(s). Each has a different role to play in helping to verify that the results are robust and trustworthy. It is generally easier to re-run the analyses using different approaches within the same original data source, but when the evidentiary bar is high, replication in alternative data sources, including the payer's own data, will likely be needed. Sharing the analytic code used for the primary RWE analysis with external parties is

another strong measure that can be taken. Some manufacturers have raised the concern that sharing of analytic code could constitute a “transfer of value” to payers raising regulatory scrutiny, and efforts are needed to clarify this point in order for true collaboration in sharing code between manufacturers and payers to proceed.

Validation by an independent third party or peer-reviewed journal publication have also been mentioned previously as ways to help verify the analyses and add to their trustworthiness. Discussion at the ICER Policy Summit suggested the broad spectrum of RWE capabilities among payers produces varying opinions about the relative usefulness of these approaches. For some payers without great depth in RWE analytic capacity, academic consultants may be very helpful in evaluating the relative credibility of externally derived RWE. For many larger payers, however, third parties, even academic faculty, paid by manufacturers to vet RWE will always be viewed skeptically, especially when payers are evaluating a manufacturer-sponsored RWE project. In addition, third parties are unlikely to have been involved in data curation and therefore may be blind to important nuances of the data sources used.

As for journal publication, payers often do use publication in highly-respected journals as a proxy for RWE quality, and there is a positive social value to peer review and publication, including the inherent check provided by external experts, broader sharing of methods and results, and the fostering of ongoing dialogue around RWE among all stakeholders. A core commitment to submitting all RWE analyses for peer-review should therefore remain a bedrock of verification. However, some caveats should be noted. As with all third parties it is unlikely that journal reviewers will know the nuances of the data source, and the timeline for peer review and publication usually fail to meet the needs of manufacturers or payers, both of whom are eager to use RWE expeditiously. Consequently, given the limits of peer review, some uses of RWE to inform

coverage and formulary decisions will need to rely on a verification process using more timely approaches that will complement eventual peer review.

Applying RWE: Making the Decision

If the contextual considerations have been discussed and a clear understanding reached of the type of assertion intended and the related need for a high or low evidentiary bar, the RWE produced should be fit for informing coverage and formulary decisions. Nonetheless, it is important to note that best practice in using RWE includes the need to integrate it transparently with other evidence sources, and to disseminate the RWE evidence as part of the justification for the decision. Clinicians, patients, and other stakeholders should be informed of the role that RWE has played, including the steps that the payer and manufacturer have taken to ensure the trustworthiness of the results.

Process Principles: Transparency, Communication, Collaboration

Underpinning each step of the development process for RWE are several critical principles that must govern the entire process. Developing RWE for coverage and formulary decisions, particularly when involving interaction between a manufacturer and payer, requires constant attention to transparency, communication, and collaboration. Methods to achieve transparency include those previously mentioned of posting RWE protocols in advance, sharing results and analytic code, and submitting work for peer review and publication. But it also includes the more subtle transparency required for effective discussion of the contextual considerations that frame the entire RWE process. Ultimately, for the benefits of RWE to outweigh its limitations and risks in applications to coverage and formulary decisions, all of these process principles must thoroughly infuse every part of the evidence generation process.

Conclusion

In concluding, it bears repeating that the environment for RWE development and use has been changing rapidly in recent years. Payers are actively analyzing their own data to seek a real world understanding of the value for money that new and old technology and medications provide. Researchers and manufacturers have new methodological tools to address some of the acknowledged RWE limitations, and they operate within a health care environment that is data hungry to distinguish the best way to care for patients and control costs across the health system. Manufacturers and payers share core goals in RWE application to decision-making, but their priorities often differ, and a mismatch between the methods used to develop RWE and the purposes and perspectives of the decision-maker is common.

The conceptual framework presented here focuses on the critical element of contextual considerations in setting the stage for successful RWE development and application. Addressed best through discussion between manufacturers and payers, the contextual considerations help define the type of evidentiary assertion that RWE will attempt to make, and the associated evidentiary bar that RWE will need to reach in order to be viewed as helpful. Knowing this, if the evidentiary needs require some form of RCT analysis, and a PCT is not practical, then developing observational RWE may be of little value. If, however, observational RWE will potentially be useful, the entire process of RWE development can be tailored to fit the decision context and the associated evidentiary bar. Guided by a shared understanding of the contextual considerations, and supported by process principles of transparency, collaboration, and communication, RWE can be developed and applied as a vital complement to other evidence in improving the care for patients in the US health care system.

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Appendix 1: Organizations Participating in the 2017 ICER Policy Summit



