

Understanding and Improving Value Frameworks With Real-World Patient Outcomes

Anupam B. Jena, MD, PhD; Jacquelyn W. Chou, MPP, MPL; Lara Yoon, MPH; Wade M. Aubry, MD; Jan Berger, MD, MJ; Wayne Burton, MD; A. Mark Fendrick, MD; Donna M. Fick, RN, PhD; David Franklin, BA; Rebecca Killion, MA; Darius N. Lakdawalla, PhD; Peter J. Neumann, ScD; Kavita Patel, MD, MSHS; John Yee, MD, MPH; Brian Sakurada, PharmD; and Kristina Yu-Isenberg, PhD, MPH, RPh

Policy makers, healthcare payers, patients, employers, and other stakeholders continue to fret about the rising cost of new medical technologies. Many scientific organizations have responded by developing new tools to assess the value of these technologies, commonly called “value frameworks.” For example, the American Society of Clinical Oncology (ASCO),¹ Memorial Sloan Kettering,² and the Institute for Clinical and Economic Review (ICER) have offered alternative approaches to assessing the value of technologies. In principle, better information about value can help moderate growth in the cost of technologies that do not provide sufficient benefit to patients.³

Yet there remains a gap between the goal of measuring value conferred to patients and the available evidence for new medical technologies. Randomized controlled trial (RCT) evidence generated for regulatory approval often incorrectly measures or fails to measure aspects of value that are key to patients. Some of these gaps and limitations are widely understood,⁴ but others have received too little attention, such as the role of patient behavior in mediating clinical outcomes.^{5,6} For example, evidence generated by RCTs often reflects outcomes achieved with motivated patients treated in environments in which individual patient behaviors that are critical to driving real-world outcomes, including adherence to medications, are controlled. As a result, interventions that improve adherence may not demonstrate large efficacy benefits in RCTs but may demonstrate larger benefits in real-world settings in which adherence is typically lower.

A working group was formed in partnership with Precision Health Economics and Intarcia Therapeutics in 2017 to make recommendations on how value frameworks should close the gap between evidence and patient behavior when evaluating new medical technologies, particularly for chronic diseases. Our working group recommended that these value frameworks enhance attention to (1) real-world evidence (RWE), (2) the role of adherence, and (3) nonclinical components of the patient experience.

ABSTRACT

OBJECTIVES: To provide recommendations that will improve approaches to measuring the value of new medical technologies to patients.

STUDY DESIGN: Informed discussion by experts after literature review.

METHODS: A working group was formed, and participants discussed how value frameworks should incorporate key features important to patients in evaluating new medical technologies, particularly for chronic diseases.

RESULTS: The working group suggests that new value frameworks should integrate real-world evidence to complement randomized controlled trials, incorporate the ways in which real-world behavior mediates outcomes, and explicitly discuss how therapies affect real-world equity and disparities in care.

CONCLUSIONS: Collective stakeholders that include key decision makers within our healthcare system need to recognize the importance of implementing real-world evidence and devote resources to further research into the chronic disease areas in which the impact of human behavior is amplified by the duration of disease and treatment.

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Overview of Value Frameworks

Unlike healthcare systems in countries such as England, Germany, and Australia, where health technology assessment processes are well established,⁷ the US healthcare system does not have a formalized approach for defining or measuring value. Private organizations have stepped in to fill this gap but offer varying perspectives and approaches. For example, ASCO has released a value framework meant to aid physician communication of cancer treatment options with patients.¹ ICER evaluates the cost-effectiveness of drug therapies from a payer and health system perspective.⁸ Memorial Sloan Kettering's drug evaluation framework, the Drug Abacus, which evaluates cancer drugs, enables users to input their own preferences on different dimensions of value.² These value frameworks differ in the perspectives that they use and in the attributes of value that they include in their evaluations. As a result, different value frameworks evaluating the same drug may have different conclusions about what may be considered reasonable value.

Recommendation 1: Value Frameworks Should Incorporate Real-World Effectiveness to Complement RCT Efficacy

Value frameworks have tended to emphasize evidence generated in RCTs, excluding or downplaying the use of RWE. Clinical trial evidence is emphasized as the gold standard for health benefit, although recently, there has been a growing awareness and movement to improve databases and infrastructure for RWE.^{9,10}

Clinical trial populations often fail to mirror real-world populations. This external validity problem is already well documented.¹¹ Clinical trials are conducted in controlled environments where the structure of the environment lends itself to optimal rates of treatment adherence.¹² More recently, some prominent researchers have argued that RCTs with smaller samples, often seen in breakthrough treatments with accelerated market approval, suffer from internal validity problems such as misalignment between the characteristics of subjects in the treatment and comparator groups.¹³

RWE can help address these limitations. To be sure, it also suffers from limitations related to internal validity (eg, persons using novel therapies in the real world are often systematically different from their peers using older drugs at the same time). Methodological solutions exist to control for some of these confounders, and more generally, care must be taken to ensure the highest degree of internal validity in RWE. However, RWE is more than just a second-best alternative to RCT evidence; it provides inferences that are necessarily applicable to real-world populations. One major area of behavior around treatment that can be captured more realistically with RWE is adherence to treatment regimens.¹⁴ Our committee recommends explicit evaluation of RWE as a potential input into value assessments.

TAKEAWAY POINTS

Steps have been taken to develop critical evaluations of drugs with the creation of value frameworks from organizations such as the Institute for Clinical and Economic Review, American Society of Clinical Oncology, and Memorial Sloan Kettering, but more work can and should be done to further refine these approaches. The Value FORWARD (Frameworks, Outcomes, and Real-World Adherence in Chronic Disease) Committee puts forth the following recommendations:

- ▶ Value frameworks should incorporate real-world effectiveness to complement randomized controlled trial efficacy.
- ▶ Value assessments must explicitly incorporate the ways in which real-world behavior mediates outcomes.
- ▶ Value assessments should explicitly discuss how therapies affect real-world equity and disparities in care.

Recommendation 2: Value Assessments Must Explicitly Incorporate the Way Real-World Behavior Mediates Outcomes

As noted earlier, a critical moderator of health outcomes outside of clinical trials is adherence. At present, adherence is not explicitly included in any value framework or in the wider body of literature of cost-effectiveness models and budget impact models. Full adherence is typically "included" as an underlying assumption in these models and frameworks, as it is implicitly a part of clinical efficacy.

The need to do this is intuitive, particularly when comparing treatments in the same therapeutic area that possess different delivery mechanisms (eg, daily oral tablets vs weekly injections) or different adverse event profiles. An evaluation of a treatment that has a positive effect on behavior and encourages a higher rate of adherence than its comparator ought to consider the clinical consequences of better adherence (eg, an improvement in patient outcomes or achievement of treatment goals).¹⁵

Adherence can also be considered an element for differentiating high-value and low-value care. Treatments that encourage improved adherence will result in less waste, because prescribed and dispensed treatments will actually be used. The importance of reducing this waste through improved adherence cannot be underestimated. Past estimates have found that more than \$100 billion annually of avoidable costs are a result of medication nonadherence.¹⁶ Explicitly incorporating adherence would enable value frameworks to better identify high-value compared with low-value care.

The magnitude of this underuse has not been well understood, in part because our current adherence measures are not sufficiently nuanced to capture the full spectrum of behavior. Current measures of adherence do not infer medication consumption and are typically used as a binary measure of "good adherence" at or above 80% or "bad adherence" below 80%.¹⁷ This threshold implies that 80% is sufficient to achieve optimal outcomes, which has not been demonstrated across all diseases. Additionally, these measures primarily capture prescription behavior (ie, whether the prescription has been submitted/picked up), not whether the person has taken the treatment.^{18,19} Further, these measures do not capture primary nonadherence for persons who do not fill their initial prescription.

Starting with chronic diseases, we should seek to map adherence patterns and link those adherence patterns to outcomes. Work that has already started in this area—for example, in individuals with schizophrenia²⁰—has demonstrated that adherence is not binary, with nuanced adherence patterns having real impacts on patient outcomes. We should seek to build on this work and develop studies that capture the value of adherence for health and quality-of-life outcomes so that adherence can be explicitly included as a separate value component in economic valuations of treatment.

Recommendation 3: Value Assessments Should Explicitly Discuss How Therapies Affect Real-World Equity and Disparities in Care

A critical aspect of treatment in the real world largely neglected by existing value frameworks is the impact on disparities in care. Previous research has demonstrated that nonclinical characteristics, such as education level, can affect adherence behaviors, which ultimately affect outcomes.²¹ Socially disadvantaged individuals are more likely to experience disease, at greater severity and with a higher likelihood of adverse effects.^{22,23} Combined with poorer adherence behaviors, disparities in healthcare can be compounded in chronic disease, where long-term consistent adherence to treatment is necessary for achieving positive outcomes. Explicitly evaluating how a new treatment can affect adherence and otherwise improve existing disparities in care would be an important element in determining the social impacts of therapeutic use.

A relatively strong body of literature already exists that articulates inequity in healthcare and some of the causes of those disparities. However, more research is required to develop methodologies to quantify and incorporate equity impacts into value assessments. It will be necessary to extend these equity concerns to additional nonclinical aspects of care, such as productivity and caregiver burden. The increased burden on productivity and caregivers also disproportionately affects disadvantaged individuals. Patients and providers have emphasized the importance of these aspects of care in making treatment decisions, but insufficient research exists to enable these aspects to play a large decision-making role. Further research and studies that take innovative approaches to, first, identifying the relevant nonclinical aspects of the patient experience and, second, measuring and quantifying these aspects are highly important to furthering our evidence base for treatment innovations and overall improving healthcare decision making.

Conclusions

A wide range of stakeholders are demanding better evidence of value. Value assessments and frameworks must adapt by making better use of real-world data and considering how individual behavior causes real-world outcomes to diverge from those seen in clinical trials. Our recommendations can help align value frameworks with value to individuals in the real world. Although we have already taken

good steps forward to develop critical evaluations of drugs, more work can and should be done to further refine these approaches. Minimally, further efforts should be made to incorporate RWE to more accurately reflect the performance of new innovations by including adherence and measuring patient outcomes in the usual settings of patient care. To do so, the collective stakeholders that comprise key decision makers of our healthcare system need to devote resources to further research in chronic diseases where the impact of human behavior is amplified by the duration of disease and treatment. ■

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Author Affiliations: Harvard Medical School (ABJ), Boston, MA; Precision Health Economics (JWC, LY), Los Angeles, CA; University of California, San Francisco (WMA), San Francisco, CA; Health Intelligence Partners (JB), Chicago, IL; University of Illinois, Chicago (WB), Chicago, IL; University of Michigan (AMF), Ann Arbor, MI; Pennsylvania State University (DMF), University Park, PA; Intarcia Therapeutics (DF, JY, BS, KY-I), Boston, MA; Dentons US LLP (RK), Washington, DC; University of Southern California (DNL), Los Angeles, CA; Tufts Medical Center (PJN), Boston, MA; The Brookings Institution (KP), Washington, DC.

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Address Correspondence to: Anupam B. Jena, MD, PhD, 180 Longwood Ave, Boston, MA 20115. Email: jena@hcp.med.harvard.edu.

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