New Patient-Derived Outcomes for Coverage Decisions

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New outcomes can capture specific aspects of disease and treatment benefits not included in traditional endpoints. These aspects can reflect change in treatment paradigms, disease course, and treatment pathways. New outcomes also need to be tailored to the patient experience, and assessment frameworks at NICE take them into consideration.

New outcomes, such as the ones derived from wearables or patient experience, are designed to capture actual value to patients and reflect changes in treatment paradigms, disease course, or treatment pathways. Four experts, who are also the authors of this article, held a panel at the ISPOR New Orleans conference in 2019 on the introduction and impact of new outcomes on coverage decisions.

What Do New Outcomes Bring? Similarities and Differences With Regulatory Decisions

With the emergence of innovative, potentially curative, and expensive treatments in the past decade, coverage and reimbursement decisions have become increasingly complex and accordingly scrutinized.

Helene Karcher introduced the topic and compared the use of new outcomes in the regulatory and reimbusement settings. New outcomes have been presented to payers and health technology assessment) bodies to make the case for coverage or reimbursement decisions. How can these new outcomes improve decision making? How much do they actually impact decisions? And what is the best way to introduce them to payers?

Second, these new outcomes can capture value to patients and caregivers, which are not always directly measured as part of routine clinical care nor considered as a clinical endpoint by regulators and payers. The patient experience is particularly of interest when products are potentially impacting on quality of life and/or the price is at parity. Moreover, payers as well as the public need to understand the added benefits of new treatments compared with potentially cheaper generic treatments. Patient experience is herein defined as benefits in outcomes that are not covered in biological realities, but rather defined by subjective experience ratings (such as treatment convenience, satisfaction, and other indirect improvements).

New endpoints historically have faced challenges at the regulatory approval stage and are now facing similar ones at the coverage decision stages. Namely, the fact that there is no precedent makes it difficult to compare new products with existing therapeutic agents. Whenever clinical trials with comparator agents have captured the new endpoints, indirect treatment comparison is only possible if a de novo head-to-head trial that includes the new endpoint is conducted comparing the new product with the existing one. For this very reason, new endpoints have been introduced and presented for regulatory decisions mainly as secondary or exploratory endpoints, with pivotal trials keeping traditional endpoints as primary.

> "...new patient-derived outcomes are starting to weigh more heavily into coverage decisions for new treatments."

Most traditional clinical trial endpoints and outcomes that measure the effect of a treatment or intervention come from daily medical practice. That is, they were designed to assess the health of a particular patient by their physician or nurse. They are a metric for "hard" clinical observations, and new outcomes can capture specific aspects of disease and treatment benefits not included in traditional endpoints. These specific aspects can reflect change in treatment paradigms, disease course, and treatment pathways. This is particularly relevant in rapidly changing treatment landscapes, such as many cancers (eg, renal cell carcinoma, prostate cancer, etc) or chronic diseases that are becoming better understood and described (eg, non-alcoholic steatohepatitis or neovascular age-related macular degeneration).

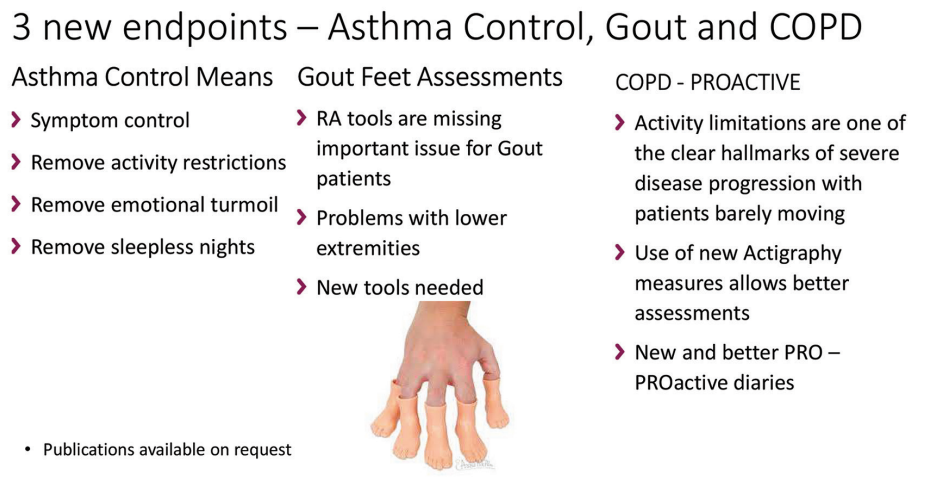
The increased attention to patient experience in their treatment journey, be it through an increase in quantitative studies or surveys, or using new clinical outcome assessments, has also triggered questions at the reimbursement and coverage decision stages about the value of treatments for patients, beyond clinical efficacy. While regulatory decisions have traditionally focused on clinical efficacy, coverage decisions are focused on value to patients, which require different patient-derived endpoints. Many health technology assessment agencies use generic preference-based endpoints, such as EQ-5D, to measure quality of life. These endpoints are critical for understanding the health benefits for a patient and the population at large—as normative population values have been obtained that may be used to evaluate population health gain. Nevertheless, these quality of life measures may lack sensitivity in some disease areas (eg, gout and ophthalmology).

Examples of Novel Patient-Centered Endpoints

Disease-specific assessments are not available in all diseases and/or may not adequately capture the patient experience undergoing new treatment. This can mean that some assessments do not capture data when the patient experiences an improvement or when patients do not answer questions completely. Unresponsiveness and/or missing data in patient-reported outcomes may lead to innovative treatments not being covered. Patients and clinical specialists often then agree to develop new methodological standards that better measure disease progression, capture patient experience, or characterize therapeutic benefit. An outcome measure that is tailored to the patient experience is often more sensitive to change under treatment (ie, is able to demonstrate treatment benefit). The results of a new treatment instrument also allow clinicians to articulate more clearly to patients and clinicians what the new treatment can offer.

In the panel discussion, Katja Rudell spoke from a perspective as a methodologist. She helped to develop 3 new clinical outcome assessments that measured disease progression better than existing measures: (1) the use of wearable actigraphy combined with symptom reduction in chronic obstructive pulmonary disease [the PROACTIVE tools]; (2) a symptom diary that captures better issues of swelling and impact of arthritis in gout; and (3) an asthma control diary that captures not only reduction in symptoms and hospitalization, but also well-being, a concept that is broader than health costs (Figure 1). All were clinical outcomes assessments derived from patients' understanding of the disease, which expanded into other areas. The discussion within the panel was centered around whether pharmaceutical companies are encouraged to consider and utilize new endpoints when standard endpoints are not fully reflective of disease progression and/or treatment impact.

Figure 1. Examples of 3 new endpoints capturing patient experiences.

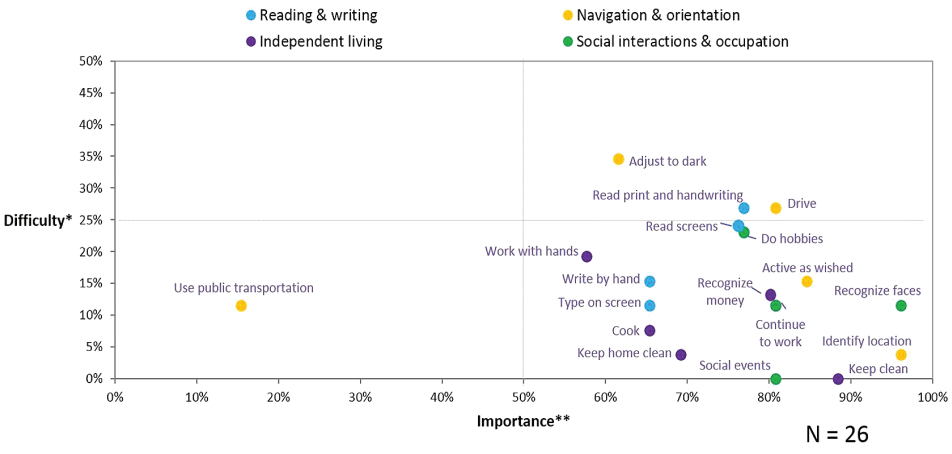


COPD indicates chronic obstructive pulmonary disease; PRO, patient-reported outcome, RA, rheumatoid arthritis.

An Industry Perspective: Using Patient Experiences to Demonstrate the Need of a New Endpoint

Stephane Regnier presented a manufacturer's perspective. Diseases are often multifaceted and current clinical endpoints might not capture all dimensions. Hence, additional endpoints can be useful. However, payers want consistency between decisions, and new endpoints can become challenging to assess for reimbursement decisions. In addition, a skeptical payer may wonder why the manufacturer decided to include a new endpoint in its

Fig 2. Importance and difficulty to perform different activities in patients with nAMD (n=26).
*** Percent of patients scoring a bit or very difficult, or stopped due to eyesight.**
**** Percent of patients scoring very or extremely important.**



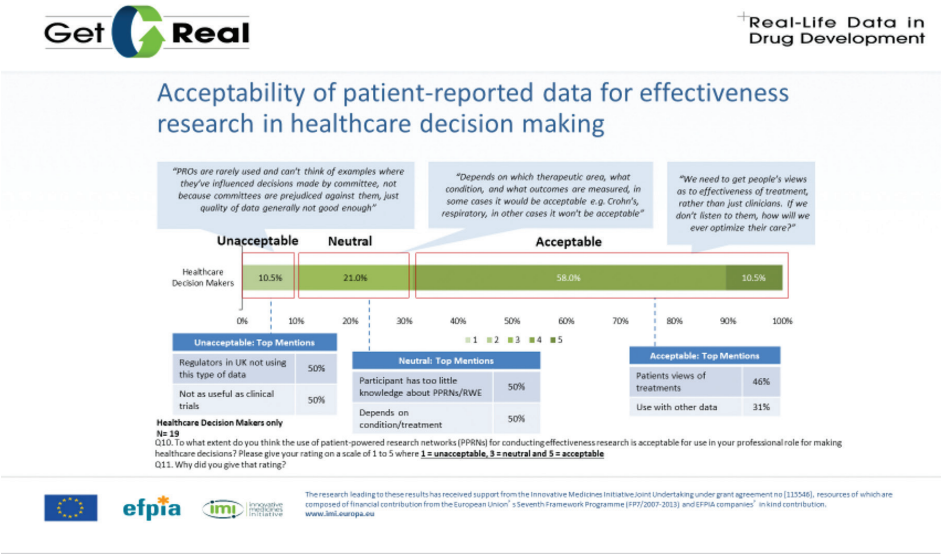
development program: is it based on scientific grounds? Or is it because the drug would not have succeeded on traditional endpoints alone? Therefore, it is critical for pharmaceutical companies to have a robust rationale to create a new endpoint. Understanding patients' experiences can provide this rationale.

Neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME) are good candidates for new endpoints. With the advent of antivascular endothelial growth factor agents[1,2] and intravitreal injection of steroids[3,4] more than a decade ago, treatment outcomes for patients have improved greatly, and vision and the quality of life of patients can be preserved in many cases.[5] However, as patients today present earlier with better baseline vision, are treated earlier, and tend to maintain but not to gain vision,[6] the best corrected visual acuity, a functional endpoint commonly used in regulatory trials in retinal diseases,[7] may no longer capture the impact of treatment in today's patients with nAMD and DME.

Multinational, individual, structured interviews were conducted with consenting patients with nAMD or DME in Canada, France, the United Kingdom, and the United States to identify activities that patients find both important and difficult to engage in. In order to demonstrate that some vision-dependent activities are impaired despite good best-corrected visual acuity, interviewed patients had moderately reduced best-corrected visual acuity <1 year (defined as ≥64 letters on an Early Treatment Diabetic Retinopathy Study chart). A total of 46 patients were interviewed; 26 with nAMD and 20 with DME.

Interviewed patients had a current average best-corrected visual acuity of 74 letters. We found that, among patients with no or only moderate reductions in their eyesight measured on standard scales, a majority still experienced difficulties with activities in their daily lives (Figure 2). This indicates a need to include additional measurements of reduced vision when assessing the impact of disease or its treatment on patients' experiences. Functional tests such as measures of contrast sensitivity, adaptation to darkness, and reading

Figure 3. A survey of European healthcare decision makers on the acceptability of patient-reported data for effectiveness research and healthcare decision making.



speed may be more useful and correlate better with patients' ability to perform important activities of daily living.

HTA Perspective on New Outcomes

Pall Jonsson presented the view on new outcomes from the health technology assessment perspective. He explained 3 different frameworks that the National Institute for Health and Care Excellence (NICE) uses for development of guidance.

The first framework is used for Technology Appraisals, which chiefly covers the assessments of drugs. The methods for Technology Appraisals[8] set out the reference case which, among other things, is intended to guide the selection of outcomes that inform the appraisal. The perspective of outcomes is to consider all direct health effects, whether for patients, or when relevant, for caregivers. NICE prefers health effects to be measured by the EQ-5D instrument reported directly from patients and converted into quality adjusted life years However, in all appraisals, a consideration is given to how relevant to patients these standard measures are in the context of the disease or the condition being appraised. Jonsson referenced a number of appraisals where the NICE appraisal committee has concluded that the full benefits of treatment have not been fully captured by the standard EQ-5D instrument, therefore highlighting the importance of new patient-derived outcomes that could help in these cases.

The second framework is used in the production of clinical, public health, and social care guidelines.[9] The nature of guidelines, usually covering much broader treatment pathways than technology appraisals, means that the scope of outcomes that are used in guideline development is broader. Quality of life using EQ-5D is always in scope, but outcomes that are specific to the condition and are deemed important to patients and caregivers are also in scope, with a special focus on core outcome sets that are specific to the disease or the condition under consideration.

The third and the newest framework is the Evidence Standards for Digital Health Technologies. This is an assessment framework that applies to digital tools in healthcare, including apps and digital clinical decision aids. While different standards apply, based on the potential the function of the technology and the risk to the users, the outcome measures reported should reflect best practice for reporting improvements in the specific condition, using validated outcome measures such as those in the COMET[10] core outcome set.

Jonsson concluded that all these assessment frameworks at NICE are open to the use of new patient-derived outcomes and endpoints. However, in all cases, it is imperative that the relevance of the outcome to patients is demonstrated and the validity and

quality of the instrument and data are established. As an indication of the appetite to use new patient-derived outcomes in the future, Jonsson presented a review conducted by the IMI GetReal Initiative[11] in which European healthcare decision makers, including those representing payers and health technology assessors, were asked about their views of patient-derived data for in their decision making. As shown in Figure 3, while a small proportion (10.5%) indicated that they would not support

> "...it is imperative that the relevance of the outcome to patients is demonstrated and the validity and quality of the instrument and data are established."

the use of these data, the majority (68.5%) took a more favorable view. The quote of one particular decision maker is inspiring and illustrates the importance of valuing what the patient values: "We need to get people's views as to effectiveness of treatment, rather than just clinicians. If we don't listen to them, how will we ever optimize their care?"

Summary

New medicinal products are under increased scrutiny for the value they provide from the patient perspective. This has led to new patient-derived outcomes starting to weigh more heavily into coverage decisions for new treatments. These new outcomes face similar challenges for validation as the ones new endpoints face at the regulatory stages. Examples in gout and ophthalmology indications show that new outcomes can be more sensitive to change under treatment than traditional endpoints and better capture the value of new treatment to patients.

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