A growing number of clinical trials now are going beyond conventional randomized control measurements to collect self-reported outcomes from patients—focusing on improving patients' involvement by including their perspectives throughout the drug development process.

But while interest in developing and applying patient-reported outcomes (PROs) across the drug development and post-market spectrum is growing—among sponsors, clinicians, payers, regulators and patients—progress has been slow.

The use of PRO measures in clinical trials is growing—an analysis of sponsor-funded interventional studies listed on CenterWatch’s Clinical Trials Listing Service found between 2005 and 2007, only 6.1% of total study procedures involved some type of subjective outcome assessment. That grew to 11.8% in the 2008 to 2010 time frame and, most recently, between 2011 and 2013 increased to 16.3% of total study procedures. PROs can capture a range of information, from symptom changes and level of functioning, to health-related quality of life and treatment satisfaction and adherence. Although their value is widely recognized, PRO use often is inconsistent and underutilized in understanding how patients feel in relation to their diseases, such as cancer, cardiovascular disease and diabetes.

The FDA does not require sponsors to consider PROs in clinical trials and, until recently, did not do much to encourage their use. However, signs point to that sentiment changing in certain drug review divisions.

“We understand that people with chronic diseases are experts in that disease, as far as the symptoms and the impact on quality of life, and what might be acceptable trade-offs on risk and uncertainty,” Janet Woodcock, M.D., director of the FDA’s Center for Drug Evaluation & Research (CDER), said in her keynote address at the RPM Report’s annual FDA/CMS Summit for Biopharmaceutical Executives last December.

The challenge for the FDA, she added, is incorporating that knowledge in a way that accurately informs regulatory decisions.

“How can we meaningfully collect that knowledge in a rigorous manner, given there’s a spectrum of opinions and a spectrum of disease burden in any given disease?” she asked.

PRO measurements often are used to evaluate products that treat chronic, disabling conditions, for which the goal of treatment is focused on alleviating the frequency, severity or duration of disease symptoms. They generally are used as primary endpoints in clinical trials in indications such as migraines and irritable bowel syndrome, in which specific symptoms play

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—Kathleen Mandziuk, scientific affairs director, late phase services at PRA Health Sciences
PROs v. clinical outcomes

But the increased reliance on PROs has not come without concerns.

One is whether subjective reported outcomes (like “feeling better”) should trump clinical outcomes. If a drug shows no hard clinical evidence of being effective, yet patients report a positive effect, how should the sponsor and the FDA treat this conflicting data?

“Most of the time, clinical outcomes will be held as the ultimate outcome in a clinical trial because they often provide more objective interpretation, increased reliability and greater simplicity of interpretation,” said Jason Cole, Ph.D., executive director, global health economics & outcome research at PPD. “However, certain disease conditions require one to consider subjective outcomes to be critically important.”

He said pain studies initially used PROs as a primary outcome in a clinical trial because attempts to obtain an objective measure of pain through a dolorimeter, a spring-loaded instrument with a gauge for measuring sensitivity to, or levels of, pain, or through a galvanic skin response lacked validity compared to simple pain scales. Other diseases, usually in neurology, such as depression and anxiety, often will have co-primary or key secondary PROs.

Subjective outcomes sometimes are difficult to evaluate because they are more qualitative in nature. So sponsors turn to an outside “adjudicator” to assess the significance of PROs between cohorts of trial participants—a situation that can increase both the cost and time of a trial.

Several CROs say the number of adjudication projects has declined in recent years because of advances in technology, while others say the biggest change has been streamlining the process to enhance their efficiency and effectiveness. Adjudication typically is required for a relatively small number of clinical outcomes assessments to address regulatory questions.

“We’ve had studies in which adjudication is involved, particularly where you are looking at some hard endpoints, such as imaging, and where an outside view on some very particular critical results requires a judgment and determination,” said Kathleen Mandziuk, scientific affairs director, late phase services at PRA Health Sciences.
“There has been a lot of progress made in the industry about how to use adjudicators more efficiently,” she said. “We use an electronic adjudication methodology that allows us to upload source documents and provide immediate viewing and processing by external reviewers. It’s an important component for certain studies, particularly if there is a concern about over- and under-reporting around safety events or for a diagnosis. So with technology, it has become more cost-effective and doable, compared to the past when it was a very large investment.”

Increased patient centricity

In giving trial participants a greater voice through PROs, sponsors and CROs also are moving toward greater patient centricity. Some industry observers predict an increase use of hand-held technology, in the form of smart phones and other devices, to assist study volunteers. However, the increased use of hand-held technology, currently used in many trials to monitor blood pressure and other concrete measures, does not lend necessarily to an increase in their use to measure PROs.

“Patient-provided devices will need more evaluation before they are used more for the collection of PROs in clinical trials, even though post-approval studies already have seen an increase in such activity,” said Cole of PPD. “It’s probably safe to say smart phones and other devices will continue to grow in use to ensure patients remain engaged in clinical trials.”

Keeping trial participants involved also is the hallmark of the publication and promotion of the FDA’s PRO guidance at the end of 2009. In 2011, the FDA took the next step, seeking multiple ways to give the patient a clear voice in clinical research by ensuring all measurements and outcomes reflect what is happening with the patient through instruments or tools, along with PROs.

“Increasingly, we are seeing patients in clinical trials saying, ‘I demand to know what is going on’ and they want to be given a greater voice, which can take many forms of greater involvement through technology,” said Jean Paty, Ph.D., senior director and practice lead-endpoint strategy for consulting at Quintiles. “Giving the patient the opportunity to have their voice, not only in trials, but also as contributing to science and to a drug product’s final label, has been a long, continuing process.”

Part of that process is determining whether the increase in the number of PROs has increased the burden on investigative sites. Whether using paper PROs that sites have to ensure are completed and then enter the data, or electronic data capture (ePRO), sites take on an added responsibility.

Some sites have their own help desks to assist patients with IT problems. Generally, larger sites can handle adding PROs more easily, while smaller sites, especially in more remote locations, can find it more challenging, said Cole.

Mandziuk said data collected directly from the patient that does not go through the sites can provide stronger information. One example, she said, is that patients can be hesitant to report outcomes if they have been asked to take a medication a certain way and have not done so.

“What are they going to be up front about that information if they have to go back to their physician and tell him, versus telling a third party independent of that physician, that they didn’t follow the rules?” said Mandziuk. “Collecting that data through specific data streams provides, in some cases, better quality. Patients will contact the independent group and not necessarily go back to their physicians for technical issues and concerns.”

Looking ahead

While using PROs is becoming critical in many clinical trials to prove safety and effectiveness to gain FDA approval, the next step for biopharmaceutical companies and payers will be to combine PROs with other observational studies to create real-world evidence (RWE).

RWE is becoming essential for sound medical coverage, payment and reimbursement decisions, according to the International Society for Pharmaeconomics Outcomes Research Real-World Data Task Force.

RWE can be used with randomized clinical trials to design more efficient trials and understand a drug’s benefit-risk profile, as well as to gain understanding of the market for launch planning, according to the task force.

“Real-world evidence shows how a drug is accepted from patients who have experience using it,” said Yin Ho, founder and CEO of Context Matters, a provider of health economics outcomes research data. “It reveals how a drug is utilized in some part of the world in policy or regulatory decisions. It’s a highly credible source of information.”

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**Percent of Total**

<table>
<thead>
<tr>
<th>Incidence of adjudicated endpoints</th>
<th>Percent of Total</th>
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<tbody>
<tr>
<td>FDA approvals</td>
<td>69%</td>
</tr>
<tr>
<td>EMA approvals</td>
<td>41%</td>
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</tbody>
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Source: Krumholz-Bahner et al. 2015; N=35 NMEs recently approved by FDA; N=88 NMEs recently approved by EMA