Commentary: Andy Smith

Why a patient's experience with a drug matters

For most pharmaceutical industry investors, the goal is to identify a company with a novel product that addresses an unmet medical need and taking a stake in that company in order to profit from a successful market launch.

For years, I was a pharmaceutical industry investor with my attention focused on a drug's market potential. This did not require an intricate understanding of how drugs get through the health technology and reimbursement reviews in order to get onto a market and treat patients. This has changed in my current position as a principal at a clinical research organisation that advises companies on pricing and market access issues.

I started my job in early 2017 and initially was comforted because we all used the same vocabulary including words like 'endpoints' 'severity' and 'target product profile.' However, as I started to work on actual projects I realised how little investors know about the barriers to commercial success that lie after a regulatory authority approves a new drug. This includes whether a patient receiving the drug actually experiences a benefit. Traditionally, doctors have been the primary source of information about the effectiveness of drugs in a real-world setting. But the organisations that decide reimbursement have moved beyond that and are now looking for 'patient-reported outcomes' which are the patient's own experience of benefit.

A patient-reported outcome measures the impact on health of the administration of a drug or use of a device, which is reported directly by the patient. The term has more recently been expanded and called a clinical outcome assessment (COA) since the latter may not have to be reported directly by the patient. And before we start listing some classic examples, let's discuss two words that may be used interchangeably – endpoints and outcomes.

I think of endpoints as typically hard numerical and clinical measurements used to determine whether a drug or device has reached a certain efficacy or safety level in comparison to those levels achieved by a placebo or a comparator, and are used for the purpose of regulatory approval. Outcomes are a larger set of endpoints that may or may not be measured in a clinical trial and may not be patient-reported.

A patient-reported outcome can be measured by a questionnaire or a typical endpoint, and enables data like pain or quality of life to be quantified. Patient-reported outcomes also lend themselves to data collection in paper or electronic diaries completed by patients.

I used to think of a traditional clinical endpoint as 'hard' and patient-reported outcomes like the activities of daily living scores as 'soft'. But do 'soft' patient-reported outcomes imply less importance to today's gatekeepers of reimbursement – the payers? If those outcomes are suicide ideation or are related to healthcare utilisation, then payers may be starting to take more notice of them than a fragile *p*-value close to 0.05 on a 'hard' clinical endpoint.

Another reason why patient-reported outcomes are becoming increasingly important is because clinical trial results, even from large well-controlled clinical studies, may reflect the best performance of a drug. By comparison, patient-reported outcomes represent real world evidence. Classic examples of these outcomes are symptoms or symptom scores ranging from the frequency of urination in benign prostate hyperplasia, to coughing in chronic obstructive pulmonary disease (COPD), to more severe and even life threatening outcomes such as on/off cycles in Parkinson's disease, seizures or pulmonary exacerbations.

Designing studies that measure patient-reported outcomes can be more complicated than those for traditional hard endpoints. When measuring the effect of antipsychotic medicines on a patient's sleeping patterns for example, the patient questionnaire needs to distinguish between the sleepiness induced by the drug on test as well as the combined effect with any co-medications and the effect of the drug on the patient's psychosis.

Who is best placed to collect, analyse and collate patient-reported outcomes to capture the effect of pharmaceutical technologies? The answer is probably charities, academic institutions and clinical research organisations that already run clinical trials.

Remarkably, the US Food and Drug Administration (FDA) has already approved drugs based on primary endpoints that were patient reported outcomes, not to mention the fact that patient-reported outcome claims have been included in the labels of 24% of the drugs approved by the FDA between 2006 and 2010.

Moreover, Germany has taken a decision to reimburse *Xalkori* (crizotinib) in non-small cell lung cancer on the basis of a patient-reported outcome after previously determining that the product offered no added benefit over the standard of care in the immature 'hard' progression-free survival data.

Since regulatory approvals no longer seem to be the gatekeeper of sales and profits that they once were, reimbursement is increasingly being weighted towards other outcomes, possibly patient-reported outcomes.

This is a quick thumbnail sketch of today's market access challenges and while patient-reported outcomes won't be the whole answer, they may help. Sponsors always need more ammunition to justify their launch price and formulary position and while some of this is provided by sophisticated health technology assessments with enormous spreadsheet models, patient-reported outcomes have already had a role in reimbursement. Did anyone ever say that the outcomes in outcomes-based contracts can't be patient based?

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