Experts raise questions about current standards of drug regulation

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A growing number of drugs are being approved on the basis of indirect ('surrogate') measures that do not always reliably predict outcomes that matter most to patients, such as living longer or feeling better.

In *The BMJ* today, experts argue that surrogate endpoints provide no guarantee of clinical benefit and should be used only as a last resort in drug trials. In a linked feature, journalists Jeanne Lenzer and Shannon Brownlee say the routine use of surrogate endpoints for drug approvals is not benefiting patients or the public purse.

Using surrogate endpoints to measure whether a new drug works can reduce the duration, cost, and complexity of clinical trials before regulatory assessment and facilitate faster patient access to new therapies, especially for chronic diseases, explain Dalia Dawoud at the National Institute for Health and Care Excellence (NICE), and colleagues.

However, the use of such endpoints can also have negative implications, such as making decisions more challenging for health technology assessment bodies, and complicating treatment decisions for patients and clinicians.

Yet they point out that over the past three decades, the proportion of clinical studies measuring the efficacy of new drugs using surrogate endpoints alone has increased from fewer than 50% in the mid-90s to roughly 60% in 2015-17. In some therapeutic areas such as cancer, surrogate endpoints account for almost 80% of all clinical studies supporting regulatory approvals.

They call for more selective use of surrogate endpoints when evaluating new drugs, restricting their use to chronic diseases, especially when collecting data on patient relevant clinical outcomes requires trials with unattainably long follow up.

And they say greater involvement of patients (and organisations representing patients) in regulatory and health technology assessment processes is also essential to ensure that the conditions for accepting surrogate endpoints for decision making are adequately met.

So should regulatory authorities approve drugs based on surrogate endpoints?

Jeanne Lenzer and Shannon Brownlee examine the US Food and Drug Administration (FDA) expedited approval process that allows drugs onto the market before their effectiveness has been proven.

Many such approvals are based on surrogate endpoints and in 2018, 73% of FDA licensed drugs (43/59) received expedited approval.

As part of the accelerated approval process, the manufacturer must conduct post-approval trials to confirm clinical benefit. If these trials show no benefit, the drug's approval can be withdrawn. But Lenzer and Brownlee say post-approval trials can be delayed for many years and the FDA has not held companies accountable when they fail to prove such benefit.

They point out that many patients are willing, if not eager, to take unproven drugs out of the belief that the FDA's approval process ensures efficacy and safety of the drugs. Doctors are also willing to prescribe based on similar beliefs.

But they argue that by allowing drugs onto the market based on

surrogates only, "the pharmaceutical industry and FDA have effectively offloaded the burden of proof onto the shoulders of the public, along with the physical harms and financial costs of clinical testing (if done at all)."

Steps can be taken to reduce the risks from using surrogate endpoints, they add, but some experts are now arguing that the use of surrogate endpoints should be restricted almost entirely to phase II studies (designed to develop hypotheses for testing and determine whether the balance of benefit to harm is sufficient to justify phase III studies).

Others disagree, saying that it would be unethical not to use surrogate endpoints and leave patients to die while waiting for new treatments.

Meanwhile, industry supports the use of surrogate endpoints, claiming it is too expensive to go back to approvals based on clinically important endpoints. But Jerome Hoffman, professor emeritus at the UCLA Medical Center says: "The final economic cost of approving and using harmful drugs is actually far greater than the cost of demanding better studies at the outset."

Surrogate endpoints focus on drug effect rather than patient benefit, and are seldom debated in patient circles, writes Roger Wilson in a linked opinion. As a sarcoma patient, he has experienced "misplaced enthusiasm" for a treatment trialled with a surrogate endpoint and approved based on a secondary endpoint. It was then withdrawn when the result was not confirmed in a later study.

"We need to reliably balance two differing viewpoints, a medical story and a parallel patient story," he says. As such, he argues that surrogate endpoints need complementary patient reported outcomes (PROs)—measures that help to build a picture of a condition from a patient perspective.

Surrogate endpoints are here to stay, he writes, but patients want to see PROs complementing them as co-primary or even sole primary endpoints. "The benefit will be that patients will understand trial results better, while the doctors guiding us to treatment decisions will have less uncertainty and stronger evidence to use."

More information: Analysis: Raising the bar for using surrogate endpoints in drug regulation and health technology assessment, *BMJ* (2021). DOI: 10.1136/bmj.n2191

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