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Should regulatory authorities approve drugs based on surrogate endpoints?

The aducanumab controversy is the latest example of surrogate endpoints failing to predict clinically important outcomes. Yet, as Jeanne Lenzer and Shannon Brownlee report, they increasingly provide the basis for drug approvals

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In November 2020, not one of the US Food and Drug Administration's 11-member advisory committee voted to approve Biogen's aducanumab for the treatment of Alzheimer's disease. When FDA administrators nevertheless went ahead with the approval on 7 June 2021,[1] three members of the committee quit in protest, sparking a national outcry.

Several media and medical journals published editorials criticising the decision, the *New York Times* and *STAT* published investigative articles about the approval process, two major hospital systems in the US announced they would not administer the drug,[2] and a national public interest group called for an independent investigation into the agency's decision. In response, FDA acting commissioner, Janet Woodcock, has ordered an inquiry, although she has defended the approval.

Beneath the brouhaha lies a deeper concern: has the FDA turned the scientific process on its head by allowing a surrogate endpoint to trump clinical trial evidence?

Accelerated pathway

Biogen had already conducted two randomised controlled trials that were stopped early because they found no patient benefit. Joel S Perlmutter, one of the advisory committee members and professor of neurology at Washington University, told *The BMJ* that when Biogen and the FDA could not find a patient benefit, they "switched tactics," focusing instead on a surrogate endpoint, a reduction in brain amyloid plaques found in a post-hoc subset analysis of one of the two trials.[3]

The FDA approved aducanumab through its "accelerated pathway," a process created in 1992 to hasten approval of "drugs that treat serious conditions, and that fill an unmet medical need." Such approvals are based on surrogate endpoints, which the agency defines as "a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit."

Surrogate endpoints stand in contrast to direct measurements of patient outcomes, often referred to as clinical endpoints, such as living longer, symptom relief, or improved quality of life. The FDA now has multiple expedited pathways. Although accelerated approval was developed for life threatening diseases without treatment options, the agency has steadily expanded its use far beyond the original intent. In 2018, 73% of licensed drugs (43/59) received expedited approval,[4] and many of those drugs treat conditions that are either non-life threatening or have existing treatments, such as gout and hypertension.

In exchange for accelerated approval, manufacturers are required to run a confirmatory study to show clinical benefits after the drug is on the market. If the confirmatory study finds no benefit, the agency has the authority to withdraw approval. The FDA states that these confirmatory trials should "ordinarily" be ongoing at the time of approval. Yet companies are taking up to a decade or longer to conduct them. In turn, the FDA rarely withdraws approval, even though some confirmatory trials are never run at all and only a small fraction confirm that the surrogate endpoint did indeed signal a clinical benefit.[5]

Critics ask: if it is so urgent to get these interventions to patients right away, why is it not equally urgent to confirm their benefits to patients instead of offering false hope at a premium price? The agency defends the use of surrogate endpoints by pointing to a handful of success stories, such as its accelerated approval of imatinib to treat leukaemia, which has proved highly effective.[6] However, the hit and miss nature of surrogate endpoints suggests their routine use for approvals is not benefiting patients or the public purse.

Root of the problem

These problems have attracted the attention of various academics and regulatory authorities. Much of their focus is on validating the predictive value of surrogate endpoints. Some non-validated endpoints may be deemed "reasonably likely" to predict a benefit. Both validated and reasonably likely surrogates can be used for expedited approvals.[7] However, even validated surrogate endpoints can be unreliable predictors of patient benefit and can fail to detect harms that exceed benefit.[3]

Surrogate endpoints can seem to be such an integral part of the disease process that they are often conflated with the disease itself, such as glucose levels and diabetes, or hypertension and stroke.

Take abnormal heart rhythms: while such rhythms can be deadly, they are, nonetheless, a surrogate outcome—myocardial infarction and death are the important patient endpoints. For more than a decade, the American Heart Association recommended lidocaine as standard treatment for patients with acute chest pain, based on the drug's remarkable ability to stop potentially deadly arrhythmias. The guidelines were subsequently withdrawn after a 1995

federally funded clinical trial found that patients treated with oral drugs related to lidocaine were 3.6 times more likely to die than those given placebo.[8]

Similarly, bevacizumab was granted accelerated approval in 2011 for metastatic breast cancer based on improved "progression-free survival"—an outcome driven by its effect on tumour shrinkage. Ralph D'Agostino, who was a scientific adviser to the FDA at the time, wrote in a commentary in the *New England Journal of Medicine*, that the FDA's acceptance of progression-free survival set a "new precedent" that could have "serious consequences."[9] The FDA subsequently withdrew approval after studies found the drug did not increase overall survival and caused life threatening harms.[10] That has not stopped the FDA from approving other treatments based on progression-free survival and tumour shrinkage.[11]

These and numerous other examples suggest a fundamental flaw regarding the use of surrogate endpoints for drug approvals (box 1). Even the FDA acknowledges that "surrogate endpoints can give misleading information about the overall risk and benefits of a medical product."[15]

Box 1: Four problems with surrogate markers

In 1996, biostatistician Thomas Fleming outlined four conceptual problems with surrogate endpoints.[12]

Non-causal associations

A surrogate endpoint that is thought to be causal might simply be associated. For example, β amyloid plaques, which are often found in the brains of people with Alzheimer's disease, are also found in a substantial proportion of cognitively intact individuals; many people with β amyloid do not progress to dementia and patients without amyloid similarly can progress to dementia before amyloid accumulation.[13] In addition, more than two dozen studies of amyloid reducing drugs have failed to show patient benefit.

Multiple causal pathways

A surrogate endpoint may lie within just one of several causal pathways of disease, thereby any changes in the surrogate may have an uncertain, and potentially negligible, effect on the desired patient outcome.

Insensitivity

The surrogate may lie within the primary causal pathway of disease and yet be insensitive to a drug's effects through another pathway that does not involve the surrogate.

Unintended outcomes

A drug or intervention may exert effects outside the disease process that can have unmeasured harms or unmeasured benefits on patient outcomes. Of the four problems, this is perhaps most under-recognised and misunderstood. By definition, surrogate endpoints, such as tumour regression or viral suppression, focus on efficacy and cannot indicate potentially harmful drug effects outside the disease process. For example, a drug might reduce cholesterol but increase non-cardiovascular mortality, as occurred with clofibrate.

Because trials using surrogate endpoints often are shorter and may include fewer participants than trials measuring clinical outcomes, adverse effects are more likely to be missed. They may even be ignored when there is an assumption that presumed clinical benefits based on a surrogate endpoint will outweigh harms. In the case of aducanumab, patients given the FDA approved dose were three times as likely to develop brain swelling and haemorrhages as patients given placebo, and were more likely to have painful headaches, vision loss, disorientation, and dizziness[14]—high risk symptoms for elderly patients, particularly those with dementia.

Inadequate confirmatory trials

Although the FDA states that confirmatory trials are intended to prove a clinically meaningful benefit, the agency has not held companies accountable when they fail to prove such benefit. Of 93 studies of cancer drugs given accelerated approval during December 1992 to May 2017, 19 simply used the same surrogate endpoint in the confirmatory study, and 20 used a different surrogate endpoint. Only 19 showed an overall survival benefit. The rest were delayed, pending, or ongoing.[16]

Lacking any consequences for delaying confirmatory trials (the FDA has never fined a company for doing so), manufacturers often put off studies for many years, or even decades. Even when confirmatory trials are concluded and produce negative results, the FDA has allowed drugs to remain on the market. Bevacizumab won accelerated approval for glioblastoma in 2009, but its confirmatory study wasn't published until eight years later. The study found no overall survival benefit but did find a significant increase in harms. Nevertheless, the drug was granted full approval for glioblastoma in 2017.[17] More recently, four other cancer drugs were left on the market after confirmatory trials failed to show benefit.[10]

Both the FDA and the UK's National Institute for Health and Care Excellence (NICE) have taken steps to categorise surrogate endpoints based on their presumed validity (box 2). However, there is reason to be sceptical of this approach. While surrogate endpoints may prove valid for certain drugs for certain indications, their narrow focus means they provide no information on patient harms. Nor can they predict efficacy for every indication in every population.

Box 2: Surrogate endpoints in England, Canada, and Germany

Although both England and Canada have accepted surrogate endpoints in their recommendations for cancer drugs, they have rejected cancer drugs approved by the FDA as lacking evidence on safety and efficacy.

Of cancer drugs recommended by the pan-Canadian Oncology Drug Review, 50% (39/78 submissions) showed an overall survival advantage, albeit a modest average gain of 3.7 months.[18] This compares with cancer drug approvals by the US FDA, in which only 20% (19/93 submissions) showed an overall survival benefit.

In the UK, NICE based 27 of 45 (60%) recommendations on surrogate endpoints.[19]

Germany uses only validated surrogate endpoints, such as viral suppression in HIV or hepatitis C, for drug approvals.

Even widely accepted surrogate endpoints can be misleading. According to the international organisation Healthy Skepticism, of 16 reported approvals based on misleading results from surrogate endpoints, eight used validated endpoints, including glucose control, cholesterol levels, and blood pressure. Each of the eight, despite positive surrogate outcomes, failed to improve clinical outcomes such as mortality and myocardial infarction.[20]

What now?

Surrogate endpoints were originally used in phase II trials to determine whether there was adequate preliminary evidence of biological effects to make a phase III trial of clinical benefits worthwhile. 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).[21]

While some countries are mandating price concessions for drugs approved based on surrogate endpoints, in the US, once a drug receives FDA approval, it is automatically included in certain clinical guidelines, such as those issued by the National Comprehensive Cancer Network. In turn, the US Center for Medicare and Medicaid Services generally covers FDA approved products.

Steps can be taken to reduce the risks from using surrogate endpoints (box 3), but some experts are now arguing that they should be limited almost entirely to their original use: as part of phase II studies. Kevin Knopf, an oncologist and member of the Institute for Health Policy at the University of California, San Francisco, believes the use of surrogate endpoints is fraught. He points to a recent study that found commonly used tumour response rates correlate poorly with overall survival.[22]

In oncology, he says, most surrogate endpoints "have not been validated to measure what matters to the actual cancer patient—overall survival or quality of life [and thus] they are 'hypothesis generating' and should be followed by a randomised phase III trial adequately powered to show overall survival."

Woodcock and others disagree, saying that it would be unethical not to use surrogate endpoints and leave patients to die while waiting for new treatments. But Jerome Hoffman, professor emeritus at the UCLA Medical Center, says this argument "reflects the all-too-common error of only looking at one side of the equation." The other side, he says, is that drugs whose harms have not been quantified can also kill patients, a problem compounded when they are left on the market after proof of lack of efficacy or harms, or both.

Industry supports the use of surrogate endpoints, claiming it is too expensive to go back to approvals based on clinically important endpoints. The question is, too expensive for whom, Hoffman 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."

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. Yet a 2016 poll—led by Aaron Kesselheim, a professor at Harvard and one of the FDA advisers who resigned in protest over the approval of aducanumab—reported that only 41 of 687 (6%) US physicians correctly answered the following question:

For a drug to get FDA approval it has to have: a) a statistically significant result; b) a clinically important result; c) both results; d) neither of the results.

The correct answer is d.[23]

Box 3: What can be done?

Doctors interviewed for this article made the following recommendations:

- Convene a panel of industry independent experts and patient representatives to define whether and under what circumstances expedited pathways are warranted
- If a drug is approved through an expedited pathway, patients must be informed that the drug or device is experimental, that benefit has not been proved, and harm could potentially exceed benefit
- Make expedited approvals provisional so that the drug or device is automatically withdrawn if confirmatory trials fail to show benefit
- Require confirmatory trials to be fully enrolled by the time the drug is approved
- Hold the FDA responsible for ensuring that clinically meaningful endpoints are used in confirmatory trials (the FDA claims this is already the case)
- Companies must provide products free or at a price no greater than manufacturing cost until a confirmatory trial is completed

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