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Surrogate end points in oncology: the speed–uncertainty trade-off from the patients' perspective

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Surrogate end points in drug regulation are thought to reduce the time required to bring new drugs to market; however, only a few of the drugs approved on the basis of these outcomes have subsequently demonstrated robust improvements in overall survival (OS). If the FDA and other regulators were to shift their priority to patient-centred outcomes, such as OS, I argue that such a shift would probably lead to fewer, but also a higher standard of drugs entering the market, potentially with faster approval decisions because novel therapies would initially be tested in later lines and in patients with a worse prognosis.

REFERS TO Forrest, R., Lagarde, M., Aggarwal, A. & Naci H. Preferences for speed of access versus certainty of the survival benefit of new cancer drugs: a discrete choice experiment. *Lancet Oncol.* **25**, 1635–1643 (2024).

The US FDA and EMA have approved more than 400 drugs (unique marketing authorizations) for patients with cancer over the past two decades[1]. Most drugs have come to market without evidence that they improve overall survival (OS) or quality of life outcomes, but because they can shrink tumours in a fraction of recipients (objective response rate, ORR) and/or delay the time until a composite end point of death and tumour reappearance (disease-free survival, DFS) or the tumour increasing in diameter beyond a defined cut-off (progression-free survival, PFS). Previous research has shown that such surrogate outcomes come with considerable uncertainty regarding the extent of benefit[2]. Not all drugs that improve PFS, DFS and/or ORR help people with cancer to live longer or have a better quality of life[3]. In fact, only 14% of drugs approved on the basis of these surrogates showed survival benefits within 4.4 years on the US market[2].

One argument suggests that using surrogate end points is beneficial because this might increase the speed with which drugs are brought to market. However, in a meta-regression analysis, my colleagues and I found that surrogates saved no time when applied to approvals in advanced-stage disease settings following disease relapse on several lines of therapy, probably because outcomes are so dire that OS can be measured just as quickly. Yet, the use of surrogates saved approximately 11 months across all settings over, on average, an 8-year drug development timeline[4]. The disadvantage of this increase in the speed of approval, of course, is greater uncertainty; but is this an acceptable trade-off? The question of whether patients are willing to sacrifice certainty for speed and, if so, by how much, animates the recent publication by Forrest and colleagues[5].

Forrest et al.[5] asked hundreds of people, about 20% of whom have or had cancer, how much certainty they would be willing to sacrifice for faster drug approvals. Their responses reveal that, on average, considerable time savings are required before people will barter knowledge. When presented with a cancer drug with an improvement on a surrogate end point but with uncertain effects on OS — a common real-life scenario — participants were willing to wait 16 months for moderate-certainty evidence and 22 months for high-certainty evidence[5]. Other data confirm these findings. A survey of more than 700 patients with multiple myeloma revealed that only half are willing to accept a novel drug being added to an established treatment backbone on the basis of PFS benefit only. The clinical scenario queried in this study is identical to that tested in the PERSEUS trial, which led to the FDA approval of daratumumab, and has been widely hailed by key opinion leaders as practice-changing[6].

Both studies suggest that regulators are getting the balance between speed and certainty wrong; they are over-prioritizing the speed at which drugs become available to access when people would, on average, rather have certainty. In this preferred scenario, the FDA would wait for more robust evidence before making a decision, rather than approving a drug on the basis of uncertain end points, such as PFS and ORR.

All of this research relies on a simplistic model of the world with or without surrogates. The counterfactual situation is more complicated, with implications for drug development and trial design and implementation. Imagine if the FDA decides tomorrow to curtail the use of surrogate end points. OS would be the new preferred end point for most indications. The aforementioned studies all assume that companies would largely run the same trial agenda, but this is unlikely to be the reality.

Initially, companies are likely to cull their drug development pipeline. The more incentive given to companies to develop drugs and the easier it is to obtain a positive trial result, the more products will enter testing. Some economists lament that cures will go missing if we change the incentive structure, although I am inclined to think that such efficiency is desirable. Many marginally beneficial and/or toxic drugs are being developed that we might be better off without, and truly transformative drugs, such as imatinib or trastuzumab deruxtecan, will continue to be developed as manufacturers will probably know that these agents

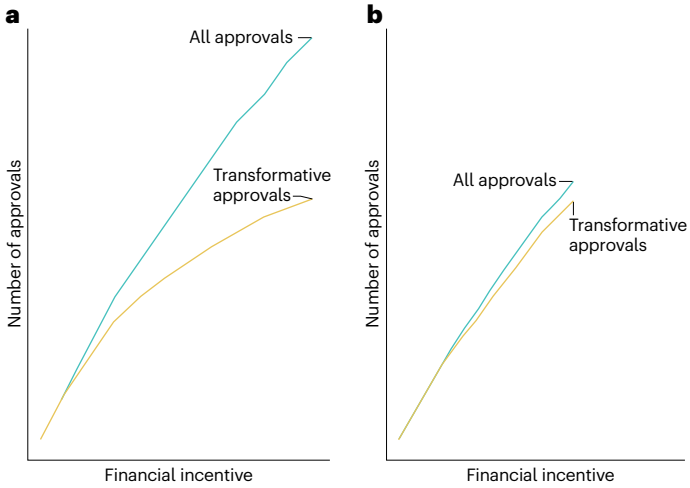

Fig. 1 | The relationship between drug approvals and financial incentives. **a**, In a world with extensive use of surrogate end points to guide approvals and ample financial incentive for drug development, transformational approvals plateau. **b**, In a world with limited use of surrogate end points, fewer total approvals occur albeit with the same, or a similar, number of transformational approvals, which continue on a linear trajectory. It is unclear which world we inhabit.

are most likely to confer robust improvements in OS and therefore receive approval.

Additionally, the entire clinical trials agenda would shift. Drug developers would be more likely to run randomized trials involving patients with relapsed and/or treatment-refractory, high-risk, advanced-stage disease, for the simple reason that these people have the worst clinical outcomes, the highest event rates and, by extension, the fastest trial results. Instead of a drug, such as pertuzumab, being initially developed alongside an existing standard-of-care in patients with newly diagnosed HER2-positive disease (the CLEOPATRA trial), we would probably see such agents first tested in women with disease progression on 1–2 prior lines of therapy. Similarly, instead of PERSEUS being run in all-comers with newly diagnosed multiple myeloma, we might see a trial exclusively enrolling patients with high-risk disease, who have a poorer prognosis and shorter life expectancy. Thus, the speed–certainty trade-off might be different. We could get more certainty and no loss of speed or, in some cases, faster approvals, with testing focused on patients who are most in need. Interestingly, the study by Forrest et al.[5] also shows that those with worse functional status are more likely to embrace speed; in a world without surrogates, more research resources, including trials, will be focused on these individuals. If trial results are positive, further trials might then be designed to test efficacy in earlier lines of therapy and/or in people with average-risk disease.

Surrogates account for the end point of two thirds of current FDA approvals and have become a major part of the canon of US drug regulation; therefore, imagining a world in which such end points are used more sparingly is currently difficult. Such a world would be different from the one we inhabit in ways beyond differing trade-offs between speed and certainty. Fewer drugs would be developed (as the barriers to market access would be higher), although hopefully development of only the most marginal drugs would be abandoned. The entire trial landscape would shift to focus on those nearing death or those with a dire prognosis. Future research should explore whether such changes would be desirable, and the attitudes of patients to such a complex counterfactual world. More research will be needed to imagine such a scenario. Pilot programmes, potentially run by the FDA or other regulatory agencies, could test the implications of more-permissive or less-permissive use of surrogates in specific disease types.

The more money we pay for cancer drugs, the easier they are to get approved and thus the more approved drugs you will have; some sort of curve probably exists that maps this relationship (Fig. 1). The FDA seems to have set up shop at one point; they seem to prioritize speed and options — a strategy that primarily benefits for-profit corporations. The core questions of whether this is what the American people and patients with cancer want, and what the shape of such a curve is and whether we are at an optimal point, have, to date, only been touched on.

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Competing interests

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