The role of imperfect surrogate endpoint information in drug approval and reimbursement decisions

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A R T I C L E   I N F O
Article history:
Received 15 December 2015
Received in revised form
28 November 2016
Accepted 2 December 2016
Available online 11 December 2016

Keywords:
Surrogate endpoints
Drug approval
Drug reimbursement

A B S T R A C T

Approval of new drugs is increasingly reliant on “surrogate endpoints,” which correlate with but imperfectly predict clinical benefits. Proponents argue surrogate endpoints allow for faster approval, but critics charge they provide inadequate evidence. We develop an economic framework that addresses the value of improvement in the predictive power, or “quality,” of surrogate endpoints, and clarifies how quality can influence decisions by regulators, payers, and manufacturers. For example, the framework shows how lower-quality surrogates lead to greater misalignment of incentives between payers and regulators, resulting in more drugs that are approved for use but not covered by payers. Efficient price-negotiation in the marketplace can help align payer incentives for granting access based on surrogates. Higher-quality surrogates increase manufacturer profits and social surplus from early access to new drugs. Since the return on better quality is shared between manufacturers and payers, private incentives to invest in higher-quality surrogates are inefficiently low.

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1. Introduction

Uncertainty surrounds every healthcare decision, particularly when it comes to approval and reimbursement decisions for novel medicines. To reduce this uncertainty, drug developers decide how much and what kind of information to collect about efficacy, real-world effectiveness, and side effects, before seeking approval or reimbursement. At the same time, regulators must decide how much and what kind of information to require before granting approval and market access. Private insurers and other payers for healthcare services must make a similar decision before deciding which therapies to cover and how to cover them.

Health economists and other researchers have studied these issues from a variety of angles. In one prominent example, Claxton et al. utilize the tools of decision theory and value of information theory to develop a framework for assessing whether enough information exists to justify adoption of new medical technologies (Claxton et al., 2005; Claxton et al., 2001). In addition, both researchers and practitioners have proposed and experimented with strategies for making sound healthcare reimbursement decisions in the presence of uncertainty about clinical benefit. For example, concepts of “conditional reimbursement” have been developed that allow payers to reimburse technologies on the basis of preliminary data and to revisit those decisions once more definitive data arrive. While such strategies are not quite commonplace, there is a growing body of evidence on when and how to deploy them most successfully (Carlson et al., 2010; Niezen et al., 2007).

In sum, researchers have analyzed the problem of decision making in the presence of incomplete information about clinical benefit, and market participants have begun to devise strategies for making decisions under limited information (Claxton et al., 2001; Claxton, 1999a; Claxton et al., 2015; Claxton et al., 2012; Claxton et al., 2016; Claxton et al., 2002; Eckermann and Willan, 2007; Eckermann and Willan, 2008; Griffin et al., 2011; Hutton et al., 2007).

At the same time, however, discomfort is growing among clinicians and payers about what they see as a slow but inexorable decline in the quality of information about new medical technologies. Increasingly, new medical technologies are brought to market on the basis of so-called “surrogate endpoint” data. For example, cancer drugs are often approved based on evidence that drugs increase “progression-free survival,” defined as the number of additional months or years until a patient’s cancer progresses to a
more severe stage. Even though progression-free survival might not be intrinsically valuable to patients, it appears to be correlated with actual survival in several important cases. (Michiels et al., 2016; Shafrin et al., 2016; Beauchemin et al., 2014) Thus, progression-free survival is used as a surrogate for, or correlate of, the outcome patients care about most. A similar example is the use of low-density lipoprotein cholesterol (LDL-C) levels as a surrogate endpoint for cardiovascular mortality (Smith, 2015).

Indeed, drugs to treat high cholesterol as well as cancer have been approved on the basis of these “surrogate endpoints.” The use of surrogates allows new drugs to be tested and approved more quickly and more cheaply. For example, it takes longer for a researcher to observe the time it takes a cancer patient to die than to observe the time it takes for their disease to progress. Thus, it would take longer to field a clinical trial measuring life expectancy than progression-free survival. Similarly, changes in LDL-C cholesterol are manifest far before cardiovascular deaths due to elevated LDL-C.

The use of surrogate endpoints continues to grow. For example, the US Food and Drug Administration (FDA) relied on surrogate endpoints in approving roughly 16 drugs per year over 2010–2014 (US Food and Drug Administration, 2015), versus roughly 6 drugs per year over 1998–2008 (US Government Accountability Office, 2009). This is perhaps to be expected as a result of progress in medicine. For example, if cancer patients have few treatment options and expect to die within months, researchers can measure final life-span more rapidly. If, however, patients live a long time when taking currently available drugs, investigators become more willing to tolerate the limitations of surrogate endpoints, in exchange for a substantially shorter or cheaper clinical trial. Malani and Philipson have identified this phenomenon of medical progress making it harder and more expensive to conduct clinical trials (Malani and Philipson, 2011).

Regardless of its underlying causes, the rise of surrogate endpoints has drawn considerable criticism charging that evidence of improvement in a surrogate endpoint should not be used to justify a claim about the effectiveness of a drug at improving patient health (Prasad et al., 2015; Fleming and DeMets, 1996; Kim and Prasad, 2016; Kim and Prasad, 2015). Since surrogates are imperfectly correlated with the final outcomes of interest, surrogate endpoint information provides weaker evidence of the benefit value than does “hard” or final outcome evidence. Yet surrogate endpoints also enable drugs to reach patients in need more quickly and potentially more cheaply.

Economic analysis can help shed some new light on this controversy. Economists will readily recognize how these issues relate to the costs and benefits associated with higher quality information (Griffin et al., 2011). We use standard economic tools to devise a straightforward and systematic framework for studying how “lower quality” surrogate endpoint evidence changes decision making about healthcare technology. In particular, this paper provides a tractable model that: (i) characterizes the benefits of higher quality surrogate endpoints; (ii) identifies the privately optimal access decisions of payers and regulators operating on the basis of imperfect surrogate endpoint information; (iii) describes the interplay between manufacturer price negotiations and the use of surrogate information; and (iv) assesses the social value of improving information quality, in light of the optimal strategies pursued by payers, regulators, and manufacturers.

Several important lessons emerge. First, we show that lower quality surrogate endpoints that are less predictive of final outcomes should lead regulators, payers, and social planners to demand greater evidence of surrogate benefit. Intuitively, decision makers substitute towards demanding a higher level of benefit when faced with a higher degree of measurement error in the clinical endpoint. As a result, measurement error reduces the expected social value from any given, newly developed drug. This in turn leads to more denials of early access and fewer new drug introductions.

Second, from a policy perspective, we show that regulators approve an inefficiently high number of new therapies while payers reimburse too few, a phenomenon that would occur even with “perfect endpoints.” While regulators and payers both value clinical benefits to patients, regulators fail to consider the economic cost of using therapy, and payers focus on the price of therapy instead of its lower marginal cost of production. However, lower quality surrogates worsen these two sources of inefficiency. Payers overreact to noise in the surrogate by demanding too much additional evidence of benefit because they fail to internalize the full benefit of allowing more drugs on the market. In contrast, regulators under react by failing to tighten evidence requirements sufficiently because they fail to recognize the full benefit of reducing the number of drugs that come to market. A practical implication of this result is that payers and regulators are most likely to disagree on access when surrogates are of low quality, resulting in lower prices to manufacturers or reduced market access. Conversely, improving the quality of surrogates creates better alignment between payers and regulators when it comes to decisions about drug approval and reimbursement.

Third, pricing and information processing decisions are connected. When price-bargaining between payers and manufacturers is perfectly efficient, payers make socially efficient decisions regarding access to new drugs. Under these circumstances, the total surplus earned jointly by payers and manufacturers reflects the true social surplus. Under efficient Nash bargaining, payers and manufacturers first maximize this joint surplus and then negotiate over how to divide it. Therefore, pricing efficiency results in social surplus-maximization, which in turn produces efficient use of the available surrogate endpoint information. Thus, an efficient pricing system helps remediate failures in the way information is processed. From a practical standpoint, inefficiencies in drug pricing and price-bargaining are numerous and widespread. However, our analysis suggests an additional benefit of mitigating these common inefficiencies.

Finally, we show that greater quality in surrogate endpoints benefits manufacturers and payers. This circumstance leads to a classic free-riding problem in which no single party has the incentive to undertake sufficient investments in improved quality. As a result of free-riding, the benefits of improved surrogates will exceed costs on the margin. Therefore, some degree of public-sector investment or subsidies for investment is called for to improve the quality of available surrogate endpoints.

While focused primarily on surrogate endpoints, our analysis also relates to the broader literature on the reliability of information about the benefit of new technologies. For example, clinical efficacy measured in clinical trials may not faithfully represent the “effectiveness” that will ultimately accrue to real-world patients because trials are conducted under constrained conditions, such as aggressive monitoring or mitigation of safety issues or adverse events (Soares et al., 2005). Outcomes in true real-world circumstances might vary from idealized randomized trial effects (Claxton et al., 2005).

Our study grows out of the decision-theoretic research that has emerged to provide a framework for evaluating the imperfect evidence available for informing adoption decisions (Claxton et al., 2005). As efforts to improve regulatory efficiency and decrease research costs continue, regulators are increasingly faced with imperfect information, one particular form being surrogate endpoints (Claxton et al., 2016; McKenna et al., 2015). Under such uncertainty, value of information analysis is particularly salient in decision making (Claxton et al., 2005; Claxton et al., 2002; Griffin et al., 2011). Regulators must consider a range of competing issues:
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