VALUE IN HEALTH ▮ (2016) ▮▮▮–▮▮▮

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Time to Review the Role of Surrogate End Points in Health Policy: State of the Art and the Way Forward

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ABSTRACT

The efficacy of medicines, medical devices, and other health technologies should be proved in trials that assess final patient-relevant outcomes such as survival or morbidity. Market access and coverage decisions are, however, often based on surrogate end points, biomarkers, or intermediate end points, which aim to substitute and predict patient-relevant outcomes that are unavailable because of methodological, financial, or practical constraints. We provide a summary of the present use of surrogate end points in health care policy, discussing the case for and against their adoption and reviewing validation methods. We introduce a three-step framework for policymakers to handle surrogates, which involves establishing the level of evidence, assessing the strength of the association, and quantifying relations between surrogates and final outcomes. Although the use of surrogates can be problematic, they can, when selected and validated appropriately, offer important opportunities for more efficient clinical trials and faster access to new health technologies that benefit patients and health care systems.

Keywords: clinical outcome assessment, health technology assessment, surrogate end points, validation.

Introduction

Market access and coverage policies for drugs, medical devices, and other health technologies ideally should be based on randomized controlled trials or systematic reviews of randomized controlled trials that assess final outcomes relevant to patients, such as survival, morbidity, and health-related quality of life [1]. Nevertheless, regulatory agencies, including the Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA), have a long tradition of licensing technologies solely on the basis of evidence of their effects on biomarkers or intermediate end points that act as so-called surrogate end points (Table 1) [2–4]. The role of surrogates is becoming increasingly important in the context of programs initiated by the FDA and the EMA to offer accelerated approval to promising new medicines. The key rationale for the use of a surrogate end point is to predict the benefits of treatment in the absence of data on patient-relevant final outcomes [5]. Evidence from surrogate end points may not only expedite the regulatory approval of new health technologies but also inform coverage and reimbursement decisions. In the United Kingdom, the National Institute for Health and Care Excellence (NICE) has made several recommendations on the basis of cost-effectiveness analyses that relied entirely on treatment effects derived from clinical trials that assessed surrogate end points [6].

Despite the potential appeal of surrogates, their use remains controversial, because they may not capture the combined benefit-risk profile of a technology and because superiority on a surrogate end point may not translate into benefits for patients, or if it did the health care system may not judge the benefits to be good value for money [7–10]. These limitations can be illustrated by the examples of two surrogate end points used in oncology

Conflicts of interest: O. Ciani and R. S. Taylor conceived the idea for this article, compiled the evidence, and jointly drafted the manuscript. All authors extensively commented on the draft and approved the final version. M. Buyse declares an association with the International Drug Development Institute, Inc., and CluePoints, Inc., and E. D. Saad with Dendrix, Ltd. All other authors declare no conflicts of interest in relation to this article. The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the agencies or organizations with which the authors are affiliated.

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1098-3015$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2016.10.011

Table 1 – Outcome and end point definitions.

End point	Definition*	Example	
		Diabetes mellitus	Cardiovascular disease
Biomarker	Characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention	HbA_{1c}, C-peptide	LDL-cholesterol, C-reactive protein, cardiac troponins
Patient-relevant (final) end point	Characteristic or variable that reflects how patients feel or function or how long they survive	Diabetic foot: mortality, health-related quality of life	Stroke, myocardial infarction: mortality, health-related quality of life
Intermediate end point	End point is, or is felt to be, of value to patients but does not represent the ultimate patient-relevant final outcome of interest	Hypoglycemic symptoms	Exercise capacity
Surrogate end point	Biomarker or intermediate end point intended to substitute and predict for patient-relevant final end point	HbA_{1c} and glucose control as surrogate for diabetes complications and mortality	SBP as surrogate for major cardiovascular events in patients with hypertension

HbA_{1c}, glycated hemoglobin; LDL-cholesterol, low-density lipoprotein cholesterol; SBP, systolic blood pressure.
* Definitions adapted from the Biomarkers Definition Working Group [5].

and considered by FDA, as a licensing body, and NICE, as a reimbursement body, in their decision-making activity.

In May 2003, the FDA approved the tyrosine kinase inhibitor gefitinib for patients with non–small-cell lung cancer on the basis of a favorable effect of the drug on the surrogate end point of the rate of tumor response [11]. The initial approved indication was the treatment of patients who were refractory to established cancer treatments—both a platinum-based regimen and docetaxel [12,13]. Nevertheless, data from two randomized studies of gefitinib versus placebo that showed no significant survival benefit became available in 2005 [14,15], and the FDA consequently released new labeling for gefitinib, which limited its use only to continuation in patients who had already taken the medicine for the disease and whose doctor believed it was helping them [16].

In a second example, the EMA approved the second-generation tyrosine kinase inhibitor dasatinib for treatment of the "chronic phase" of chronic myeloid leukemia (CML) in patients who were newly diagnosed and positive for the Philadelphia chromosome [17]. This approval was based on data from a randomized controlled trial that showed the relative efficacy of dasatinib compared with imatinib on the primary end point of confirmed complete cytogenetic response (CCR, surrogate outcome) by 12 months (e.g., 77% vs. 66%; $P = 0 \cdot 007$) [18]. In deciding about approval of new products, however, EMA considers their benefit-risk profile, whereas decisions of health technology assessment (HTA) bodies and payers such as NICE and the Centers for Medicare & Medicaid Services in the United States are based on a broader value-for-money evaluation. When NICE appraised the drug in March 2012, it concluded that first-line use of dasatinib for the treatment of CML represented poor value for money. In a situation in which clinical effectiveness information was available either in terms of biomarker end points or as immature data on overall survival, the evidence review group systematically looked for evidence supporting the adoption of CCR at 12 months as reliable predictors of overall survival by looking at data of patients treated with tyrosine kinase inhibitor, naive to previous pharmacological therapies for CML. Historical data of midterm survival (i.e., up to 7 years since the start of the treatment), conditional to achievement of CCR at 12 months post-treatment, were identified and used to predict and extrapolate long-term survival curves for the dasatinib-treated cohort of patients. The analyses showed a small estimated incremental gain in survival (final outcome) extrapolated from the observed improvement on CCR (22.7 years vs. 21.3 years) and a patient cost of £30,477 per year, which equated to a cost per quality-adjusted life-year (QALY) of more than £200,000 [19].

Because the issues introduced are likely to intensify in a context of promotion of accelerated approval for medicines, raising greater challenges for those bodies seeking to assess the costs and benefits of new health technologies, in this policy perspective we discuss the case for and against the use of surrogate end points, give an overview of methods to validate the selection of surrogates, and propose a framework for the appropriate use of surrogates by policymakers. Finally, we identify unanswered questions and key areas for future research.

The Case for Surrogate End Points

Results from surrogate end points generally accrue more quickly than from final end points, thus allowing for clinical trials with shorter follow-up periods and smaller sample sizes [20]. Reducing trial sample size and duration ensures faster patient access to new therapies and it means that trials are also less expensive, which make surrogate end points attractive to manufacturers or research sponsors alike. This efficiency can be illustrated in the setting of cardiovascular disease, for which the most common final patient-relevant end points are mortality and major cardiovascular morbidity (e.g., myocardial infarction, stroke, and hospitalization due to angina). The rates of these final outcomes are, however, typically low, particularly in populations with early-stage cardiovascular disease, thus requiring a definitive trial involving thousands or tens of thousands of patients followed up for several years. In contrast, a trial powered on a surrogate primary end point (e.g., carotid artery intima-media thickness and luminal loss) might involve a few hundred patients followed up for weeks or months [21]. Primary end points are often discrete, whereas surrogates are usually continuous and often repeatedly measured, thus providing more statistical power to detect significant treatment effects [22]. It is, however, important to note that smaller sample sizes restrict the likelihood of