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The proper use of surrogate end points in research

In the performance of clinical research, one attempts to explain or predict relationships among variables. Generally, at minimum, there are at least two variables: an intervention (exposure or predictor or independent variable), and an outcome (disease occurrence or dependent variable). Developments of disease, disability, or death are often outcomes of clinical interest. In rare events, or when the outcome is far off in the future, clinical trials require a large number of participants to be followed for a long time. This is costly. It is sometimes not feasible, or ethical, to wait for the development of the outcome of interest. Studies utilizing surrogate end points can be useful in ascertaining the effects of treatment without waiting for the clinical end point of interest to develop. However, caution must be exercised when using surrogates and when applying the results of surrogate end points to the outcome of interest.¹

A SURROGATE END POINT is a laboratory measurement or physical sign that substitutes for the true, clinically meaningful outcome of interest. Surrogate end points simply attempt to measure a future event with a short-term event. Studies based on surrogate end points, however, are less reliable than studies with the end point of interest. Schatzkin and Gail note that surrogates may be unacceptable because the quality of evidence they provide is less than that obtained by directly

studying the effects of the intervention on the outcome one is truly interested in.¹ However, sometimes the quality of evidence provided by surrogates is adequate; and, it is important to know when the use of surrogate is appropriate and when it is not.¹

SURROGATE END POINTS FAIL for many reasons. Sometimes the surrogate is not in the clinical pathway of the disease process. There may be several clinical disease process pathways and the intervention may affect only the pathway mediated through the surrogate, giving the false impression that the intervention has a favorable effect on the outcome of interest. Or, the surrogate may be insensitive to an intervention effect, giving the false impression that the intervention has no effect on the outcome of interest. Also, the surrogate may fail because the intervention may have mechanisms of action independent of disease process.²

The use of surrogate end points is most appropriate when certain criteria are met. The relationship between the surrogate end point and the corresponding clinical end point should be well-established, both qualitatively and quantitatively. Furthermore, an estimate of the expected clinical benefit should be derivable from the estimate of the reduction in incidence of the surrogate end point. Finally, the surrogate end point should be easier to measure than the corresponding clinical end point and in general be more frequent.²

SOME EXAMPLES of surrogate end points follow. Elevated BP is often used as a surrogate for cardiovascular-related mortality. Tumor regression is a frequently used surrogate end point in cancer treatment trials. And perhaps one of the more recognizable uses of surrogate end points is measuring CD4+ cell counts in HIV/AIDS infection.

OTHER CONCERNS with using surrogates in lieu of end points of interest have been raised. As early as 1996, Flemmings and DeMets described their apprehension

TABLE 1. Support for surrogate use

Factor	Favors surrogate	Does not favor surrogate
Biological plausibility	Epidemiologic evidence extensive, consistent, quantitative; credible animal model; pathogenesis and drug mechanism understood; surrogate late in causal path	Inconsistent epidemiology; no animal model; pathogenesis unclear; mechanisms not studied; surrogate earlier in causal path
Success in clinical trials	Effect on surrogate has predicted outcome with other drugs in class and in several classes	Inconsistent results across classes
Risk-benefit/public health considerations	Serious or life threatening illness and no alternative treatment; large safety database; short term use; difficult to study clinical end point	Less serious disease; little safety data; long term use; easy to study clinical end point

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regarding surrogate use in phase III clinical trials.² One example they use is the Cardiac Arrhythmia Suppression Trial (CAST).³ At the time of this study, premature ventricular contractions (PVCs) were thought to be a good surrogate for ventricular tachycardia or ventricular fibrillation and thereby for sudden cardiac death (SCD). Many antiarrhythmic agents available at the time or being developed reduced PVCs, and it was assumed that this would benefit the outcome of interest—SCD. CAST was proposed to test the hypothesis that these antiarrhythmic agents did actually reduce SCD, and this occurred with some furor about the ethics of the study since a placebo control was part of the study design. In fact, it turned out that the antiarrhythmic therapy not only failed to reduce SCD but in some cases increased its frequency.

The controversy over the appropriateness of surrogate use continues. In August 2007, FDA advisor Clifford J. Rosen, MD, recommended discontinuing use of surrogate end points for approval of drugs to treat type 2 diabetes after findings from ADOPT (A Diabetes Outcome Prevention Trial) demonstrated that patients were at increased risk for heart failure and cardiovascular ischemia after taking a drug that was approved on the basis of surrogate data.⁴

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IN SUMMARY, it should be understood that most (many) potential surrogate markers used in clinical research have been inadequately validated and that the surrogate marker must fully (or nearly so) capture the effect of the intervention on the clinical outcome of interest. In addition, many if not most treatments have several effect pathways, and this may not be realized, particularly early in the research into a given intervention. Finally, one important downside to the use of surrogate measures is a result of their strength—that is, the ability they offer to use smaller sample size and shorter trials to gain insight into the benefit of an intervention. This is because smaller and shorter-term studies result in the loss of important safety information. Nonetheless, the use of surrogate end points is sometimes necessary, and Table 1 summarizes some of the issues that favor support in using a surrogate.⁵ **JAAPA**

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