Validated Surrogate Endpoint

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Definition

An endpoint supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate endpoint predicts a specific clinical benefit. A validated surrogate endpoint can be used to support marketing approval of a medical or tobacco product in a defined context without the need for additional studies to demonstrate the clinical benefit directly. Although the term has been used in a conceptually broader way, from a U.S. regulatory standpoint, a validated surrogate endpoint almost always refers to a biomarker.

Examples

- Hemoglobin A1c (HbA1c) reduction is a validated surrogate endpoint for reduction of microvascular complications associated with diabetes mellitus and has been used as the basis for approval of drugs intended to treat diabetes mellitus.
- HIV-RNA reduction is a validated surrogate endpoint for human immunodeficiency virus (HIV) clinical disease control and has been used as the basis for approval of drugs intended to treat HIV.
- Low-density lipoprotein (LDL) cholesterol reduction is a validated surrogate endpoint for reduction of cardiovascular events and has been used as the basis for approval of statins and other LDL-lowering drugs such as PCSK9 inhibitors and ezetimibe.
- Blood pressure reduction is a validated surrogate endpoint for reduction in rates of stroke, myocardial infarction, and mortality and has been used as the basis for the approval of drugs and in pivotal trials of medical devices intended to treat hypertension.
- Serum uric acid reduction is a validated surrogate endpoint for improvement of gout symptoms and has been used as the basis for approval of drugs to treat gout.

Explanation

This glossary makes a distinction among three categories of endpoints under consideration to serve as surrogate endpoints (i.e., validated surrogate endpoint,
reasonably likely surrogate endpoint, and candidate surrogate endpoint). The categories describe use of the endpoints for regulatory decision making in the U.S., based on the level of clinical validation. This discussion considers the use of “validated surrogate endpoints” in this context.

Randomized clinical trials testing the efficacy of new medical interventions that use as a primary endpoint a measure of clinical benefit provide the highest level of evidence for a clinical benefit, but the time and resources to demonstrate benefit on the endpoint directly are often substantial. Usually effects on surrogate endpoints are appealing because they can be detected far more rapidly or easily, or potentially less invasively, than the effect on a clinical outcome and often with far fewer patients. In situations where there is no effective treatment for a serious illness, use of surrogate endpoints can bring new therapeutics more quickly to those who need them. Validated surrogates have also proven useful for evaluation of new drugs in established drug classes, such as anti-hypertensives, diabetics, and HMGCoA reductase inhibitors, where outcome studies against placebo would be unethical and non-inferiority studies with certain clinical outcomes would be very long, costly and potentially infeasible. In addition, validated surrogate endpoints have been used to assess harm (e.g., Hy’s Law as a predictor of hepatic toxicity or QTc prolongation as a predictor of TdP arrhythmias).

Biomarkers provide a rich pool of candidate alternative endpoints, but in order for a biomarker to be considered a validated surrogate endpoint in a specific clinical context, there must be evidence to demonstrate that an effect on the surrogate endpoint reliably predicts the clinical effectiveness of a medical product. This is important in a regulatory setting, as a validated surrogate endpoint can be used as the basis for approval of a medical product without the need for additional studies to demonstrate the clinical benefit. Generally, required evidence includes a combination of a clear mechanistic rationale and in most cases, data from multiple randomized clinical trials showing that the effect on the surrogate endpoint predicts the effect on the clinical outcome of primary interest. Observational studies can provide supportive data for the surrogate endpoint’s validation, but cannot prove etiology, causation, or mechanism and therefore generally cannot alone validate a surrogate endpoint.

Historically there have been examples of mechanistically plausible surrogate endpoints supported by epidemiologic findings that have not predicted a clinical benefit in controlled clinical trials. For example, after an acute myocardial infarction, a number of ventricular premature beats per hour greater than 10 is a strong predictor of an increased risk of sudden death. The Cardiac Arrhythmia Suppression Trials (CAST 1 and 2) used the drugs encaïnide, flecainide, and ethoszine to substantially lower ventricular premature beats (VPB) rates, but the three drugs markedly increased mortality. This example illustrates that correlation between a biomarker and the endpoint intended to assess clinical benefit across individuals (i.e., the biomarker is a “correlate”) is necessary but not sufficient to conclude that the biomarker is a validated surrogate endpoint that can be used as a replacement for the endpoint intended to assess clinical benefit in clinical trials (i.e., the biomarker is a “trial-level” surrogate endpoint). This phenomenon might
occur because therapies have multiple mechanisms of action or have unanticipated, or “off-target,” effects that have different impacts on various endpoints. Tumor response as an endpoint in cancer clinical trials provides an illustrative example. Anti-cancer therapeutics may work through a variety of mechanisms, including killing dividing cells or promoting cell death, suppressing cell division, and reducing tumor cell motility or invasion capability. A drug that is effective in shrinking a tumor will not necessarily be effective in destroying tumor cells that are capable of disseminating throughout the body and invading distant organs. The drug might also cause harmful side effects, through its influences on normal cells, that negatively affect patient survival. Therefore, the tumor response endpoint provides an incomplete picture of the overall effects of an anti-cancer drug, and the partial effects captured by tumor response may differ across drugs. Consequently, although a tumor response endpoint will tend to correlate with endpoints intended to assess clinical benefit such as survival (i.e., individual patients who respond live longer than those who do not respond) and may be helpful to detect initial signals of drug activity, it cannot generally be relied on for traditional approval to predict clinical benefit for use in clinical trials evaluating therapy efficacy.

There are, however, some cases in which the biomarker is directly in the disease pathway or is the disease itself. In such circumstances, the surrogate endpoint may be considered a validated surrogate endpoint, sometimes even without extensive empirical clinical evidence.

1. Declining kidney function manifests as elevated serum creatinine and decreased glomerular filtration rate and is often progressive. When this occurs in renal disease due to conditions such as diabetes, hypertension or autoimmune disease, reduction in the decline of renal function has been accepted as a validated surrogate endpoint for evaluation of treatments intended to slow the rate of decline of renal function. Two angiotensin receptor blockers, losartan and irbesartan were shown to have such an effect. In the studies that showed this effect, longer follow up also showed a reduction in the rate of end stage renal disease.

2. In the treatment of hepatitis C, because progression of liver disease occurs over a long period of time, clinicians use sustained virologic response (SVR) to determine treatment success and it is considered a virologic cure. Sustained virologic response 12 weeks after treatment (SVR12) has been considered a validated surrogate and is used as the primary endpoint in clinical trials based on numerous observational cohorts showing strong correlations between SVR assessed at earlier and later time points and multiple clinically important outcomes.