Surrogate Endpoint: Alternative for Early Assessment of a Potential Treatment Effect

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ABSTRACT

The efficacy of health technologies, medicines and medical devices should be demonstrated in trials that evaluate final patient-relevant outcomes such as survival or morbidity. We provide a summary of the present use of surrogate end points in health care policy, discussing the case for and against their reviewing and adoption validation methods. Although the use of surrogates can be problematic, they can be validated and selected properly, offers important chances for more efficient clinical trials and faster access to new health technologies that benefit health care systems and patients. In early drug development studies, tumor response is often the true primary endpoint. Usually clinical trials are needed to show that it can be dependent upon to predict, or correlate with, clinical benefit in a context of use. Surrogate endpoints that have undergone this ample testing are called validated surrogate endpoints and these are accepted by the Food and Drug Administration as evidence of benefit. Choosing the right surrogate endpoint and proving that it can predict the intended clinical benefit, however, is not always straightforward. When a disease has been sufficiently studied, surrogate endpoints can measure the underlying cause of a disease (such as low thyroxine levels and hypothyroidism) or an effect that predicts the ultimate outcome (such as measuring diuresis, which is expected to improve symptoms of heart failure).

Keywords: Surrogate endpoint, Clinical trials, Oncology

Introduction:

In the development of a pharmaceutical product, a clinical trial is the major part conducted for the demonstration of efficacy and safety of the product. The measurement used to assess the effect of the treatment is termed as endpoint. Endpoints used to measure clinical benefit, such as reduction of mortality rate and prolongation of survival time, are usually considered “true” endpoints because clinical benefits are the ultimate purpose of a medical treatment. However, the practicality and feasibility of measuring a “true” endpoint may be limited because of various reasons. Therefore, it is important to have some alternative measurement that would allow early assessment of a potential treatment effect.

A surrogate endpoint is a biomarker that coordinates very well with the activity and toxicity of the molecule. It is generally an acceptable endpoint for registration of a molecule with regulatory agencies. A biomarker qualifies as a surrogate endpoint for a clinical endpoint after controlled clinical trials which show a statistically and clinically significant correlation between the two. Surrogate endpoints must reliably speculate both the safety and efficacy associated with a pharmacological agent.

Surrogate endpoints are sometimes obtained from studies evaluating the natural history of the epidemiology. There are few examples of surrogate endpoint such as blood pressure is an accepted surrogate endpoint for anti-hypertensive agents as it predicts cardiovascular disease, heart failure, stroke and kidney failure [1]. For example, for several classes of agents bone mineral density has shown to have a good correlation with fracture rates. However, this has not turned out to be the case for fluoride [2].

The limitations of “true” endpoints prompted the use of surrogate endpoints. Surrogate endpoints that are considered to relate clinically important outcome but does not in itself measure a clinical benefit. This surrogate plays a particularly important role in the early development of a pharmaceutical product, when surrogate endpoints can be used to demonstrate if the drug has any pharmacological effect, as postulated by the in vitro model or in preclinical in vivo studies.
A surrogate is mainly useful if it is easily measured and highly correlated with the true endpoint. Often, 'true' endpoint is one with the clinical importance to the patient. For example, a major clinical outcome or mortality, while a surrogate is one biologically closer to the process of disease, for example, ejection fraction. Use of the surrogate can often lead to dramatic reductions in sample size and much shorter studies than use of the true endpoint [3].

Atkinson [4] has compiled a table of biomarkers which have found varying degrees of clinical utility. Tables 1

<table>
<thead>
<tr>
<th>Biomarker / surrogate endpoint</th>
<th>Type of drug</th>
<th>Clinical endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>Antihypertensive Agents</td>
<td>Stroke, atherosclerosis, Heart failure</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>LDL lowering statins</td>
<td>Coronary artery disease, heart attacks</td>
</tr>
<tr>
<td>Viral RNA</td>
<td>Antiretroviral agents</td>
<td>Survival, decrease in infections</td>
</tr>
<tr>
<td>HbA1C, Glucose</td>
<td>Antidiabetic agents</td>
<td>Diabetic neuropathy</td>
</tr>
<tr>
<td>CD4 T cells</td>
<td>Antiretroviral agents, cytokines</td>
<td>Sustained reduction in viral RNA</td>
</tr>
<tr>
<td>Intraocular pressure</td>
<td>Antiglaucoma agents</td>
<td>Preservation of peripheral vision</td>
</tr>
<tr>
<td>Bone mineral density (BMD)</td>
<td>Antosteoporotic agents</td>
<td>Fracture rate</td>
</tr>
<tr>
<td>MRI (Magnetic Resonance Imaging) Scans</td>
<td>Agents for treatment of Multiple Sclerosis (MS)</td>
<td>Decrease in rate of progression disease (check PDR)</td>
</tr>
<tr>
<td>CT (Computed tomography)</td>
<td>Anticancer agents</td>
<td>Survival</td>
</tr>
<tr>
<td>Scans for tumor size</td>
<td></td>
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</tr>
</tbody>
</table>

Surrogate Endpoint related to Oncology:

Surrogate endpoint in oncology is widespread and increasing. The strength of association between the surrogates used and clinically meaningful outcomes is often weak or unknown. Attempts to validate surrogates are rarely undertaken. When this is done, validation relies on a fraction of available data, and often concludes that the surrogate is poor. Alternatively, if a drug fails to improve quality of life or overall survival, market authorization is rarely revoked [5].

The most frequently used surrogates are response rate; a set of criteria distinguishing tumor shrinkage; and time to event endpoints, such as progression-free survival (PFS) or recurrence-free survival (RFS). Progression-free survival and Recurrence-free survival are composite endpoints, where an event is explained as either growth of tumor beyond an arbitrary threshold (progression) or detectable recurrence of disease, or death. While there is debate as to whether PFS is intrinsically meaningful [6] since patients do not feel when they cross the arbitrary threshold of ‘progression,’ we believe that PFS is strictly speaking, a surrogate.

Surrogate endpoint related to cardiovascular disease:

A commonly used example in the cardiovascular disease is cholesterol. While elevated cholesterol levels increase the cause of heart disease, the relationship is not linear - many people with normal cholesterol develop heart disease, and many with high cholesterol do not. A clinical trial may show that a drug effective in reducing cholesterol, without showing directly that it prevents death. Proof of its efficaciousness in reducing cardiovascular disease was only presented five years after its original introduction, and then only for secondary prevention [7].

Are surrogate endpoints important for medical product development? [8]

When a surrogate endpoint clearly specifies a beneficial effect through appropriate studies, its use commonly allows for more efficient drug development programs. For example, many clinical trials, using a range of different blood pressure lowering medications, have demonstrated that reducing systolic blood pressure reduced the risk of stroke. Hence, quantification of reduction, surrogate endpoint of systolic blood pressure can stand in for the clinical outcome of stroke, and clinical trials targeting the reduction of risk of stroke that can be conducted more rapidly in smaller populations using this validated surrogate endpoint.

- Why use a surrogate endpoint?
  - Faster and easier to study,
    - e.g. Cholesterol or Blood Pressure vs. Stroke, Survival, Myocardial infarction.
  - Faster drug development,
  - Cheaper,
  - Proving effect on direct endpoint may not be practicable.
- Very low event rates – use of the surrogate in common clinical practice may make definitive trial seem unethical [9].

Examples of Surrogate Endpoints: [9]

- Hypertension – arterial blood pressure: surrogate for Cerebrovascular accident, Myocardial Infarction, heart failure
  - Hypercholesterolemia –surrogate for atherosclerotic disease basing on cholesterol levels.
  - Human Immunodeficiency Virus (HIV) – CD4 count or viral load: surrogate for complications of HIV
  - Glaucoma – surrogate for loss of vision is intraocular pressure.
  - Diabetes Mellitus – blood glucose / haemoglobin A1c surrogate for complications.

Limitations of using Surrogate endpoint:

On yielding potentially important advantages, the use of surrogate endpoints, sometimes can show inappropriate results and thus causes problems. The two principal concerns on introduction of any proposed surrogate variable are it may not be true estimation of clinical outcome of
interest. For example, surrogate endpoint may measure the
treatment activity associated with one of a specific
pharmacological mechanism, but it may not provide exactly
complete information on the range of actions and ultimate
effects of the treatment whether it is positive or negative.
There have been many examples where treatments showing
a highly positive effect on a proposed surrogate have
ultimately been shown to be detrimental to the subjects of
clinical outcome; conversely, there are cases of treatments
conferring clinical benefit without measurable effect on
proposed surrogates. Some of the cancer treatments
provide a positive effect in a treatment in surrogate
endpoint, but a detrimental effect on a patient health. In this
case, although a treatment may achieve a certain degree of
tumor shrinkage, the toxicity of the drug itself may in fact
worsen a patient’s general health and thus shorten survival
time.

Regulatory Requirements:
The Food and Drug Administration (FDA) must balance
engaging needs in its approach to assess biomarkers, and it
must do so with limited resources. On one hand, biomarkers
are viewed as a route to reduce the cost and time required to
develop effective new drugs, devices, and biologics to
address chronic diseases; on the other hand, patients and
consumers must be protected from risks associated with
biomarker use. The perceptible efficiency dichotomy also
applies to the use of biomarkers in health claims for foods,
which the Food and Drug Administration regulates under a
different framework than is applied to biologics, drugs and
devices.

Validating a Surrogate Endpoint
• For a surrogate to be useful, the relationship between
the surrogate and the “direct” endpoint must be
strongly established. Simple correlations, no matter
how strong, are not enough.
• The ideal method is the analyses of many studies of
known effective drugs, which evaluated both the direct
and surrogate endpoints, in order to establish (and
quantitate) the relationship.
• Very difficult to identify what type and quantity of data
are sufficient to adequately validate a surrogate for use
as a primary endpoint in a Phase 3 trial.
• Once proved, a surrogate may be useful for future
studies of medicines, particularly those with same
mechanism of action.

Conclusion:
Post-marketing studies, planned to protect drugs have
meaningful benefits, are often not performed. The potential
for surrogate end points to have an impact on health care
policy and the consequent diffusion of technologies into
practice is illustrated by the fact that the primary outcome of
more than 40% of pivotal trials used as the basis for
approval of new indications is a surrogate that aims to
substitute for and predict a final patient – relevant outcome.
The strength of association between the surrogates used and
clinically meaningful outcomes are often unknown or weak.
Attempts to validate surrogates are rarely undertaken. In
both the cases surrogates must be used only when continuing studies examining hard end points have been fully
enrolled. Relying on surrogates rather than final patient –
relevant outcomes increases the uncertainty when making
decisions about licensing and coverage of health care
technologies. The use of appropriately validated surrogate
depth points, however, provides an unmissable opportunity to
speed up access to innovative technologies that offer
important benefits for patients and health care systems and
to improve efficiency within the research and development
environment.

References:
1) A.V. Chobanian, The influence of hypertension and other
hemodynamic factors in atherogenesis, Prog Cardiovasc. Dis.
2) B.L. Riggs, S.F. Hodson, W.M. O’Fallon, E.Y.S. Chao, H.W.
Wahner et al., Effect of fluoride treatment on the fracture rate
322 (1990), 802–809.
3) Wittes J, Lakatos E, Probstfield J, Surrogate endpoints in
4) A.J. Atkinson Jr., Physiological and laboratory markers of drug
C.E. Daniels, R.L. Dedrick, C. Grudzinskas and S.P. Markey, eds,
5) Surrogate endpoints in oncology, Robert Kemp and Vinay
Prasad; BMC, 2017.
6) Booth CM, Eisenhauer EA. Progression-free survival:
meaningful or simply measurable? J Clin Oncol. 2012;
30:1030–3.
changes and reduction in the incidence of major coronary
heart disease events in the Scandinavian Simvastatin Survival
8) https://www.fda.gov/drugs/development-
resources/surrogate-endpoint-resources-drug-and-biologic-
development
9) Clinical Trial Endpoints, Eugene J. Sullivan, MD FCCP, Food
and Drug Administration, https://www.fda.gov/media/84987.
10) ICH Harmonized Tripartite Guideline; Statistical Principles of
Clinical Trials, 52.26, 1998
11) Perspectives on Biomarker and Surrogate Endpoint
Evaluation, Douglas Balentine, Thomas Fleming, Philip