Challenges of Surrogate Outcomes

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Definition of Surrogate Outcome

(very) weak sense (Wittes et al, Statist Med 1989)
An endpoint measured in lieu of some other so-called ‘true’ endpoint. A surrogate is especially useful if it is easily measured and highly correlated with the true endpoint.

weak sense (FDA's Qualif. process for drug development tools)
A biomarker intended to substitute for a clinical efficacy endpoint. Surrogate endpoints are expected to predict clinical benefit (or harm).

Because there is substantial risk of adversely affecting the public health if a biomarker is falsely accepted as a surrogate endpoint, robust scientific evidence is needed to justify qualification of a biomarker for broad use as a surrogate.
Definition of Surrogate Outcome

strong sense (Prentice, Statist Med 1989)

A response variable for which a test of the null hypothesis of no relationship to the treatment groups under comparison is also a valid test of the corresponding null hypothesis based on the true endpoint.

Key features

1. Treatment dependent (i.e. we would not use BP as surrogate for statins or PCSK-9s)
2. The rates of outcome (i.e. CVD) are independent of treatment conditional on the surrogate process (i.e. the effect of statins or PCSK-9s would have to be fully mediated by their effect on cholesterol)
## Desirable Characteristics of Surrogates


<table>
<thead>
<tr>
<th>Austin Bradford Hill's guidelines increasing the likelihood of causative association</th>
<th>LDL-C</th>
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<tr>
<td><strong>Strength</strong></td>
<td>A strong association between marker and outcome, or between the effects of a treatment on each</td>
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<td><strong>Consistency</strong></td>
<td>The association persists in different individuals, in different places, in different circumstances, and at different times</td>
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<td><strong>Specificity</strong></td>
<td>The marker is associated with a specific disease</td>
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<td><strong>Temporality</strong></td>
<td>The time-courses of changes in the marker and outcome occur in parallel</td>
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<td><strong>Biological gradient (dose-responsiveness)</strong></td>
<td>Increasing exposure to an intervention produces increasing effects on the marker and the disease</td>
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<td><strong>Plausibility</strong></td>
<td>Credible mechanisms connect the marker, the pathogenesis of the disease, and the mode of action of the intervention</td>
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<td><strong>Coherence</strong></td>
<td>The association is consistent with the natural history of the disease and the marker</td>
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<td><strong>Experimental evidence</strong></td>
<td>An intervention gives results consistent with the association</td>
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<td><strong>Analogy</strong></td>
<td>There is a similar result to which we can adduce a relationship</td>
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Challenges of Surrogate Outcomes

Depending on the definition adopted, they either require a trial with the actual outcome or they may not work.

Some “famous” failures of “weak” surrogates

1. HDL-C and CETP-inhibitors
   i) Torcetrapib. In the ILLUMINATE trial it increased HDL-C by 72% and decreased LDL-C by 25%, yet increased the risk of CV events by 1.25 (95% CI: 1.09, 1.44) and the risk of all-cause mortality by 1.58 (95% CI: 1.14, 2.19). It also increased SBP by a mean of 5.4 mmHg.
   
   ii) Dalcetrapib. In the dal-OUTCOMES trial it increased HDL-C by 31 to 40% and had a minimal effect on LDL-C. Trial stopped for futility with hazard ratio for a CV composite of 1.04 (95% CI: 0.93, 1.16) and no effect on all-cause mortality.
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2. Glucose
   i) In the ACCORD trial, intensive glucose lowering (metformin, rosiglitazone and other agents) led to a reduction in glycated hemoglobin from 8.1% to 6.4% versus 7.5% in the intensive versus standard therapy arms, respectively. The hazard ratio for a CV composite was 0.90 (95% CI: 0.78, 1.04) but all-cause mortality was significantly higher in the intensive therapy, HR = 1.22 (95%: 1.01, 1.46), so the intensive treatment was discontinued early.

   Currently, FDA requires that glucose-lowering agents demonstrate no increase in CV risk.

Numerous examples of failed surrogates exist outside cardiology – for example, progression free-survival as a surrogate for all-cause mortality in oncology.
Do surrogates ever work?

Some successes of surrogates:
1. LDL-C and statins – reduction in LDL-C translates into reduction in CV risk
2. SBP and various antihypertensive agents
3. LDL-C and ezetimibe - reduction in already low levels of LDL-C translates into further (albeit modest) reduction in CV risk
Conclusions

Given empirical evidence of multiple failures of weak surrogates, it appears that one cannot help but follow the Prentice definition.

This implies the necessity of outcomes trials for new compounds.

In some situations, where strong surrogacy has been established, new products in the same class could rely on surrogates (some examples in CV devices).

Weak surrogates can be used for preliminary studies as done currently.